From: Robert Carlson
Sent: Wednesday, October 12, 2011 2:31 PM
To: bioeconomy@ostp.gov
Subject: size of US bioeconomy

Dear OSTP,

Please find attached a recent report from Biodesic that estimates current US revenues from genetically modified products.

Best Regards,

Rob Carlson

Robert Carlson
Principal, Biodesic
Seattle, WA
www.biodesic.com

Biodesic 2011 Bioeconomy Update

Rob Carlson

Genetically modified (GM) crops continue to see extensive global adoption. Revenues are growing rapidly and are substantially larger than commonly reported. Within the United States, more than 50% of cropland is now planted in GM seed resulting in 2010 revenues of nearly $110 billion. Together with 2010 revenues from biologics of $75 billion and revenues from industrial biotechnology of $115 billion, I estimate that total 2010 revenues from genetically modified products exceeded $300 billion, or the equivalent of more than 2% of Gross Domestic Product (GDP).

U.S. GM Crop Revenues

Farmers continue to adopt GM crops in the United States. As of 2009, approximately 50% of U.S. cropland was planted with GM seed[1]. GM corn, cotton, and soy have all reached approximately 90% market penetration, which may represent the saturation point for these crops (Figure 1). Sugar beets have achieved similar levels of penetration just two years after market introduction. New guidelines from the U.S. Department of Agriculture (USDA) that allow companies seeking approval of GM crops to prepare their own environmental impact studies may speed up the introduction of new strains[2].

Clarifying the Economic Benefits of GM Crops

Sufficient experience with GM crops now demonstrates solid evidence of yield improvements and reductions in primary inputs such as fuel, water, and chemicals (Figure 2). Internationally, a summary of peer-reviewed surveys of farmers in 12 countries found average yield increases generally in the range of 20–30% across multiple strains of GM corn, soy, and cotton[3]. One recent study estimated that on 10 million acres, Bt corn provides the following benefits: $231 million additional revenue from yield gains, a reduction in use of 5.5 million pounds of insecticide, a reduction of 5.5 million gallons of water from reduced insecticide application, a reduction in 70,000 gallons of aviation fuel not used in insecticide application, and improved environmental conditions for non-target organisms and wildlife[4].

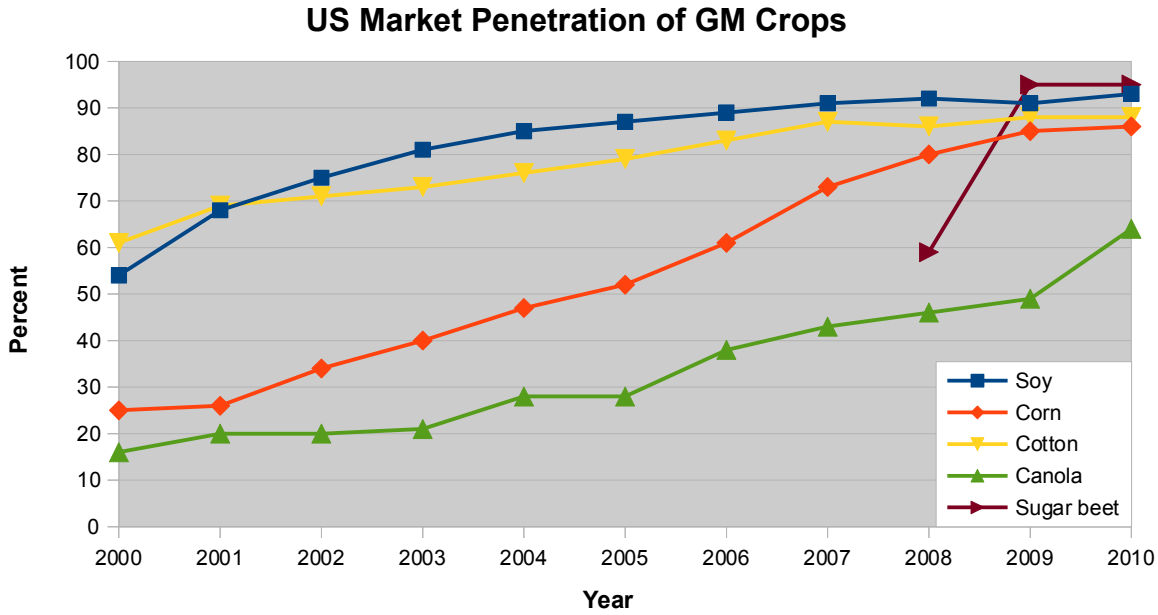


Figure 1: Acreage of GM crops has been increased rapidly, with GM corn, soy, cotton, and sugar beets reaching >90% market penetration. Source: USDA.

The realization of specific yield increases often depends on environmental factors such as the sandiness and moisture content of the soil, which affect the viability of pests and their larvae.

Adoption of GM crops often brings substantial additional benefits. For example, the use of Herbicide Resistant (HR) strains is correlated with an adoption of reduced-till or no-till practices, which result in increased soil carbon and nitrogen content[5]. Moreover, the use of Bt corn has resulted in regional declines in the European corn borer population that are estimated to have saved growers of non-Bt corn $3.9 billion over 14 years[6].

Despite growing evidence of economic benefits, contradictory reports continue to emerge regarding the overall economic impacts of GM crops. These discrepancies occur in large part due to differences in how pesticide use is recorded (for example, by total volume or by active ingredient volume) and similar experimental issues, although a literature review by the National Research Council found substantial variation in performance and yield across different farms and different crops[7]. Given the variability in assessing crop performance, I feel the best indicator of the farm scale benefits of GM crops is simply the continued use and increased adoption by farmers worldwide.

> *The best indicator of the farm scale benefits of GM crops is simply the continued use and increased adoption by farmers worldwide.*

Proof of demand by farmers can be found in 1) the increase in acres planted and 2) the increase in composite seed price indices of between 30 and 100% for GM corn, soy, and cotton seeds. The price increase includes the effects of demand and greater value (seed plus insecticide in one package, for example)[8]. Finally, farmers also report substantial labor savings (20–30%) from using GM crops in reduced application of pesticides or weed management[9]. For small farmers, in particular, this labor savings can be monetized by using this time for off-farm employment, thereby further amplifying the indirect benefits of planting GM crops.

Putting the Numbers Together

GM Crops

Revenues from GM crops are growing rapidly and are substantially larger than generally reported. A diverse range of publications continue to confuse revenues from GM seed sales

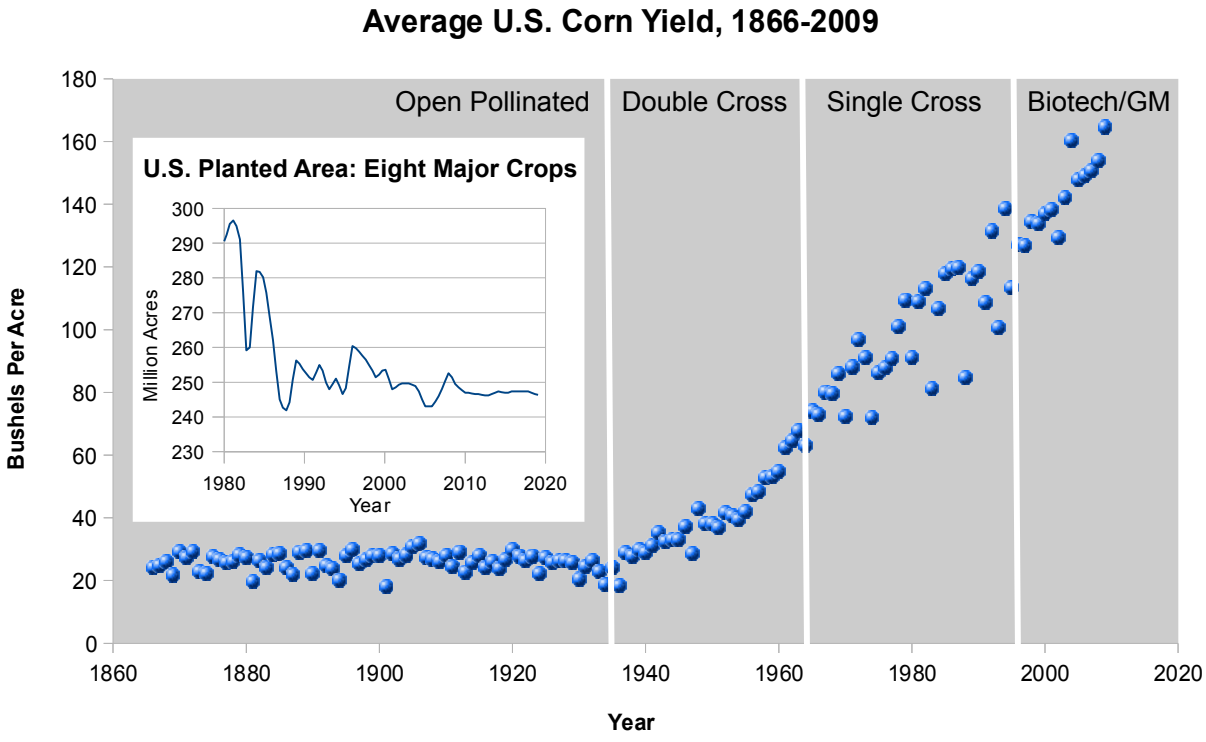


Figure 2: Corn yield improvement over eight decades through breeding and genetic modification. Inset: Total U.S. land under cultivation has declined over the last 30 years[10].

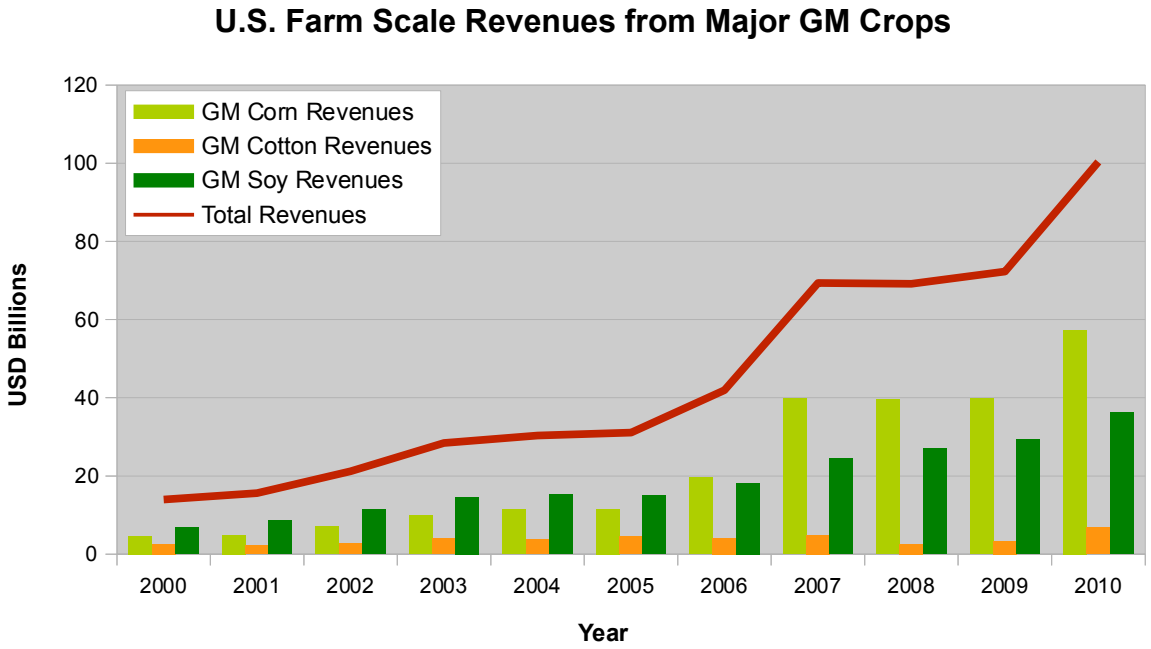


Figure 3: Farm scale revenues from GM corn, soy, and cotton. Source: USDA.

with actual farm scale revenues from GM crops. In 2010, global revenues from GM seeds and associated licensing amounted to $11.2 billion, approximately half of which was in the United States[11]. The sale of GM crops at market, however, earned substantially more. The three largest crops—GM corn, soy, and cotton—earned $100 billion in U.S. farm scale revenues in 2010 (Figure 3). I estimate that GM sugar beets contributed just over $1.5 billion[12], with GM papaya, canola, and other crops contributing roughly another billion dollars. This brings total U.S. revenues of GM seeds and crops to over $105 billion. Continued increases in GM crop acreage in the next few years will certainly raise the total, with revenues from GM alfalfa contributing $1–2 billion dollars next year assuming planting is not again halted by lawsuits.

U.S. 2010 revenues from GM crops was just under $110 billion.

Biologics

Other sub-sectors of the bioeconomy are also growing rapidly. Estimates of global revenues from biotech drugs (biologics) continue to vary widely, ranging from $48 to $138 billion[13]. In 2010 half this revenue, and about half the annual growth, was generated within the United States[14]. Biologics constitute an ever larger share of annual drug approvals, reaching 28% in 2010, largely due to a multi-decadal declining trend in small molecule approvals[15]. Assessing the sub-sector is complicated by the fact that approximately 85% of companies selling biologics are private, accounting for 50% of employment and 27% of sector revenues, with these figures derived from surveys rather than publicly transparent sources such as financial filings[16]. Based primarily on financial filings of public companies, I estimate that 2010 U.S. revenues from biologics were approximately $75 billion.

U.S. 2010 revenues from biologics were approximately $75 billion.

Industrial Biotechnology

Revenues from industrial biotechnology, here defined as fuels, materials, chemicals, and industrial enzymes, continue to display the most rapid growth within the bioeconomy. However, while data on revenues from biologics and GM crops is relatively easy to come by, the same cannot be said for industrial biotechnology. This dearth of quality data is in large part due to the lack of reporting mechanisms for the biotech industry at the level of most national governments; the data that exists is instead collected by private consulting firms and through voluntary surveys by such organizations as the OECD. Data on other economic activity in the United States is generally gathered via the North American Industrial Classification System (NAICS). NAICS codes are used by the Department of Commerce to attribute employment and revenues to those sectors of the economy for which codes are

defined. There are, however, no codes specifically identifying biotechnology-related businesses.

U.S. 2010 revenues from industrial biotechnology were at least $115 billion.

The methodology used here to assess revenues from industrial biotechnology involves surveying multiple reports from governments and private consulting firms and then removing contributions from products that are not obviously derived from genetic modification, such as biodiesel or chemicals purified from natural sources[17]. In particular, it is challenging to disentangle the portion of revenues due to so-called "bio-based chemicals", which to date are unlikely to be substantially derived from genetically modified systems. Various sources put "bio-based chemicals" at 5–10% of total chemical sales as of 2010. Contributing to the challenge, total global chemical sales are reported in the range of $1.8 to $3.2 trillion, a spread of nearly a factor of 1.5. The largest contribution to increasing U.S. revenues from industrial biotech in 2010 was an approximately 30% increase in ethanol sales[18]. Extending prior revenue figures in the subsector, I estimate that 2010 U.S. revenues from industrial biotechnology were at least $115 billion[19].

Revenues are likely to climb sharply starting in 2011 with the market introduction of chemicals, fuels, and co-products such as cosmetics from firms such as Solazyme, Gevo, and Amyris. In particular, I estimate that chemicals produced by the new wave of genetically modified microbes could see sales of nearly a billion dollars next year.

The three aforementioned companies are the most discussed, but many companies that began life as venture capital-funded "biofuels" companies in 2005–2008 have come to the inevitable realization that competing in the global liquid fuels market will be challenging. Consequently, while these companies refine their production processes to reach profitable production of fuels with retail values of ~$1/L, they are beginning to enter markets for higher-value petrochemical replacements that sell for $10–1000/L. The next five years will bring many more entrants into this market, particularly as barriers to entry fall with decreasing costs of modifying and using organisms to produce biochemicals that are drop-in replacements for petrochemicals[20].

And So Goes the World...

Governments around the world see biotechnology as an opportunity for economic development and a route to increased independence and influence. In addition to major investments by growing economic powerhouses India and China, countries such as Indonesia, Pakistan, and Brazil are intent on developing domestic biotech research and development capabilities. Malaysia has bootstrapped itself from receiving none of it's GDP from biotech in 2005 to a self-reported 2.5% as of 2010. Table 1 displays estimates of 2010 biotech revenues, estimated growth, and 2020 target revenues for selected countries[21].

Developing economies are rapidly harvesting the fruits of this investment. Nearly 50% of GM crops are grown in developing countries, with a 17% annual increase compared to 4% for industrialized countries[22]. Yield improvements are thus accumulating faster in developing countries, and increased global yields of GM cotton have contributed to a decrease in price that is reportedly causing California growers to rotate away from cotton to more profitable crops[23]. Growth in revenues from biologics suggests that developing economies are poised to generate substantial value in this sub-sector as well; China's 2010 contribution of 5% of global sales growth is more than double the share of sales themselves[24]. In industrial biotechnology, in addition to substantial domestic investment in technology development, many emerging economies are able to import skills and technology in the form of partnerships with companies looking to use abundant local biomass to generate renewable fuels and chemicals.

The next five years will see a substantial increase in such products entering global markets. New players will emerge constantly, en-

Country	2010 Biotech Revenues	2010 Est. Growth	2020 Target Biotech Revenues
Malaysia	2.5%	25%	10%
China	2.5%	20%	5–8%
United States	>2%	10–15%	NA
India	0.24–0.40%	20%	1.6% (2015)
Pakistan	1.6%	<5%	NA
Europe	<1.0%	5%	NA

Table 1: Biotech Revenues as Share of GDP. Source: Biodesic.

abled in large part by falling cost barriers and proliferating skills and infrastructure[25]. Upcoming Biodesic Technical Notes will focus on global biotechnology investment and shifts in the scale of production as small companies begin to compete directly in petrochemical markets.

About the Author:

Rob Carlson

Rob Carlson is a Principal at Biodesic, LLC, an engineering, design, and consulting firm in Seattle, WA. At the broadest level, Rob is interested in the future role of biology as a human technology. He has worked to develop new biological technologies in both academic and commercial environments, focusing on molecular measurement and microfluidic systems. Carlson is the author of the book “Biology is Technology: The Promise, Peril, and New Business of Engineering Life”, published in 2010 by Harvard University Press, which was named to Best Books of 2010 lists by *The Economist* and the writers of *Foreign Policy*. Dr. Carlson earned a doctorate in Physics from Princeton University in 1997.

Notes

1 The Impact of Genetically Engineered Crops on Farm Sustainability in the United States, NAS/NRC, 2010, pg. 30.
2 "New self-reporting for GM crops", Lucas Laursen, Nature Biotechnology 29, 558 (2011)
3 Peer-reviewed surveys indicate positive impact of commercialized GM crops, Janet E Carpenter, Nature Biotechnology 28, 319–321 (2010)
4 NRC, pg. 139
5 NRC, pg. 70
6 NRC, pg. 87
7 NRC, pg. 150
8 NRC, pg. 147
9 NRC, pg. 174
10 Sources: USDA-NASS; Troyer, Crop Science 46.2 (2006): 528; Rupert and Butzen, Crop Sci, 19(2).
11 Global Status of Commercialized Biotech/GM Crops: 2010, Clive James, ISAAA, 2011.
12 Based on 2010 USDA figures for 95% GM sugar beet penetration and an 8% increase in total harvest over 2009.
13 What's fueling the biotech engine—2009–2010 Saurabh Aggarwal, *Nature Biotechnology*, 28(11), November 2010; "Top 30 Biologics 2010 ", R&D Pipeline News, La Merie Business Intelligence. www.bioportfolio.com; Bullish On Biologics, Scientific American Worldview, http://www.saworldview.com/article/bullish-on-biologics
14 "Top 30 Biologics 2010 ", R&D Pipeline News, La Merie Business Intelligence. www.bioportfolio.com
15 Fresh from the biologic pipeline—2010, Jim Kling, *Nature Biotechnology*, 29(3), March 2011
16 *Biology is Technology: The Promise, Peril, and New Business of Engineering Life*, Robert Carlson, Harvard University Press, 2010.
17 *Biology is Technology*, 2010.
18 Ethanol Facts: Economy, Renewable Fuels Association, http://www.ethanolrfa.org/pages/ethanol-facts-economy
19 *Biology is Technology*, 2010.
20 See *Biology is Technology*, 2010; "Microbrewing the Bioeconomy: Innovation and Changing Scale in Industrial Production", R. Carlson and R. Wehbring, Biodesic Technical Note 20110210_01, http://biodesic.com/library/Microbrewing_the_Bioeconomy.pdf; "The New Biofactories", R. Carlson, *What Matters*, McKinsey Publishing, 2009, http://whatmatters.mckinseydigital.com/biotechnology/the-new-biofactories.
21 Biodesic will soon release a report further elaborating global investment in biotechnology.
22 James, 2011.
23 NRC, pg. 162
24 Bullish on Biologics, 2011.
25 *Biology is Technology*, 2010; "Microbrewing the Bioeconomy", 2011.

From: Saleem H. Ali
Sent: Sunday, October 16, 2011 3:19 PM
To: bioeconomy@ostp.gov
Subject: Your new initiative

Greetings

I am intrigued by your new initiative as it ties in with much of my research as well.

Attached is a proposal I have been working on regarding sustainable livelihoods given the "jobs versus" environment debacle in Washington.

Would welcome your thoughts if this overlaps with your interests.

Warm regards
Saleem

_____

Saleem H. Ali, Ph.D.
Professor of Environmental Planning and Asian Studies Rubenstein School of Environment and Natural Resources Director, Institute for Environmental Diplomacy and Security James M. Jeffords Center for Policy Research University of Vermont

Sustainable Livelihoods Assessment: An Industrial Ecological Approach to Reconciling Jobs and the Environment

Saleem H. Ali

Professor of Environmental Planning, University of Vermont
Adjunct Professor, Brown University Watson Institute for International Studies

Proposal to the Institute for New Economic Thinking (INET), Fall, 2011

Summary

How can we integrate ecological sustainability criteria from "mines to markets" in economic development planning for particular industrial development paths in order to match natural strengths in supply of resources regionally with demands for particular products and services? This proposal seeks to develop a novel tool that utilizes methods from industrial ecology and complex systems science to assist in planning for industrial development that is most ecologically suitable for a particular unit. Unlike contemporary approaches that focus on "green jobs" within a new economy, the proposed research will focus on innovations within existing industrial sectors to assist them in planning for a more economically efficient and ecologically sustainable labor profile.

Introduction: Relevance to INET RFP and Core Competencies

Growth in natural systems is always considered an intermediate step towards stability. Organisms grow during certain stages of development and then after maturity stabilize in terms of physical criteria as well as their ability to consume resources. Indeed, unfettered growth in natural systems is considered a disease – the pathology of cancerous cells stems from their uncontrolled growth. However, in the mantra of modern economics it is assumed that growth is essential for well-being, largely because of a need for constant livelihood.

The field of "sustainable economics," which has been identified by INET as one of six thematic areas for this grant cycle, grapples with ways to consider economic growth in the context of human livelihoods. Furthermore, INET has also identified "human capacity and economic development" as a priority area. The proposed research will explore ways to develop an integrated assessment methodology for charting the environmental and social impact of a particular industrial development decision using techniques from the emerging field of industrial ecology such as life cycle analysis and combining them with conventional economic techniques for measuring labor impact such as economic multipliers.

Much of the epistemic conflict between environmental science and economics is premised on a contention between job creation and environmental regulation. The central challenge to reconciling jobs and the environment is the tension between durable resource development, which generally supports ecological metrics, and disposable product development which supports more reliable employment. The proposal will also consider the role of hybrid livelihoods in some regions that allow for subsistence resource acquisition (eg. Having household gardens and energy supply) alongside a globalized model. Earlier work on "sustainable livelihoods" has been focused on local development efforts by donors

rather than understanding the full context of employment in the production and consumption of goods and services. This research proposes using methods from the emerging field of industrial ecology to compare development paths based on particular investments in product or service dispensation. The metrics could also be provided to consumers as an additional mechanism for "constructive consumption."

The partnership between INET and CIGI is particularly appealing and appropriate for this proposal since any planning methodology requires a strong governance interface. Once the assessment methodology has been developed, governments would be invited to apply the tool for particular industrial plans in partnership with business. My affiliation with the World Economic Forum as one of their "Young Global Leaders for 2011" will also be helpful in this regard.

The University of Vermont, where I am based has developed a core capacity in the study and application of novel approaches in economic analysis through the Gund Institute for Ecological Economics. Furthermore, my partnership with scholars at leading research centers in Industrial Ecology such as the Yale School of Forestry and Environmental Studies will provide an opportunity to refine the methods needed to develop a sustainable livelihoods assessment tool.

Such a tool would radically change how economic development planning decisions are made on the supply side and inform consumers about choices regarding goods and services on the demand side.

Historical Context

Economists have successfully branded themselves as scientists with mathematical exactitude who can artfully negotiate the vagaries of human consumption patterns through pricing mechanisms. Yet the life support systems that sustain the planet have eluded their grasp, and often been relegated to the residual category of externalities. Given the resistance of conventional economics to consider ecological constraints directly, a parallel field of ecological economics had to develop, led by a few rebel researchers. Most notably, the Romanian-American economist Nicholas Georgescu-Roegen, who had been a protégé of Joseph Schumpeter, dared to embrace other physical sciences, such as physics and biology in his analysis of the economy as part of a complex ecological system. His seminal book *The Entropy Law and the Economic Process* (1971), was the first treatise to consider physical constraints on economic growth.

In the last decade there seems to be a promising shift across the tectonic plates of economic thought that just might close the fault lines. Ecological economists have moved closer to pricing strategies that have been the pulse of conventional economic analysis. For example, to conserve a wetland, they are now making the case for how the ecosystem provides an economic service of preventing property damage from hurricanes or naturally cleaning effluent. While they might not have accurate pricing for "nature's services" at this stage, at least they are trying to delineate monetary indicators in tangible terms rather than using the polemics of priceless value (Kareiva et al, 2011).

At the same time, conventional economists are also beginning to think outside their hallowed box and

consider the consequences of neglecting ecological constraints. However, economic growth still remains sacrosanct to mainstream economists. While there is little doubt that economic growth is necessary for developing countries to climb out of poverty, what is less clear is the necessity for economic growth in mature economies where population is also stabilizing. A troika of inertial forces has prevented our move forward in addressing this issue. The first part of the challenge is an assumed need for growth in order to sustain technological innovation. However, pathways to innovation can also be found through constraints and resource scarcity and end-user innovation (von Hippel, 1994). Second, is the questionable assumption that links economic growth to quality of life that has been challenged among others by Nobel laureate Daniel Kahneman (inter alia, 2003). Third there is an incipient reluctance from the global economic system to grapple with the question of inequality of wealth. On the issue of inequality, environmental sustainability advocates also have a checkered record since they often advocate local insularity (McKibben, 2008) even though international trade is well established as the most potent antidote to global inequality.

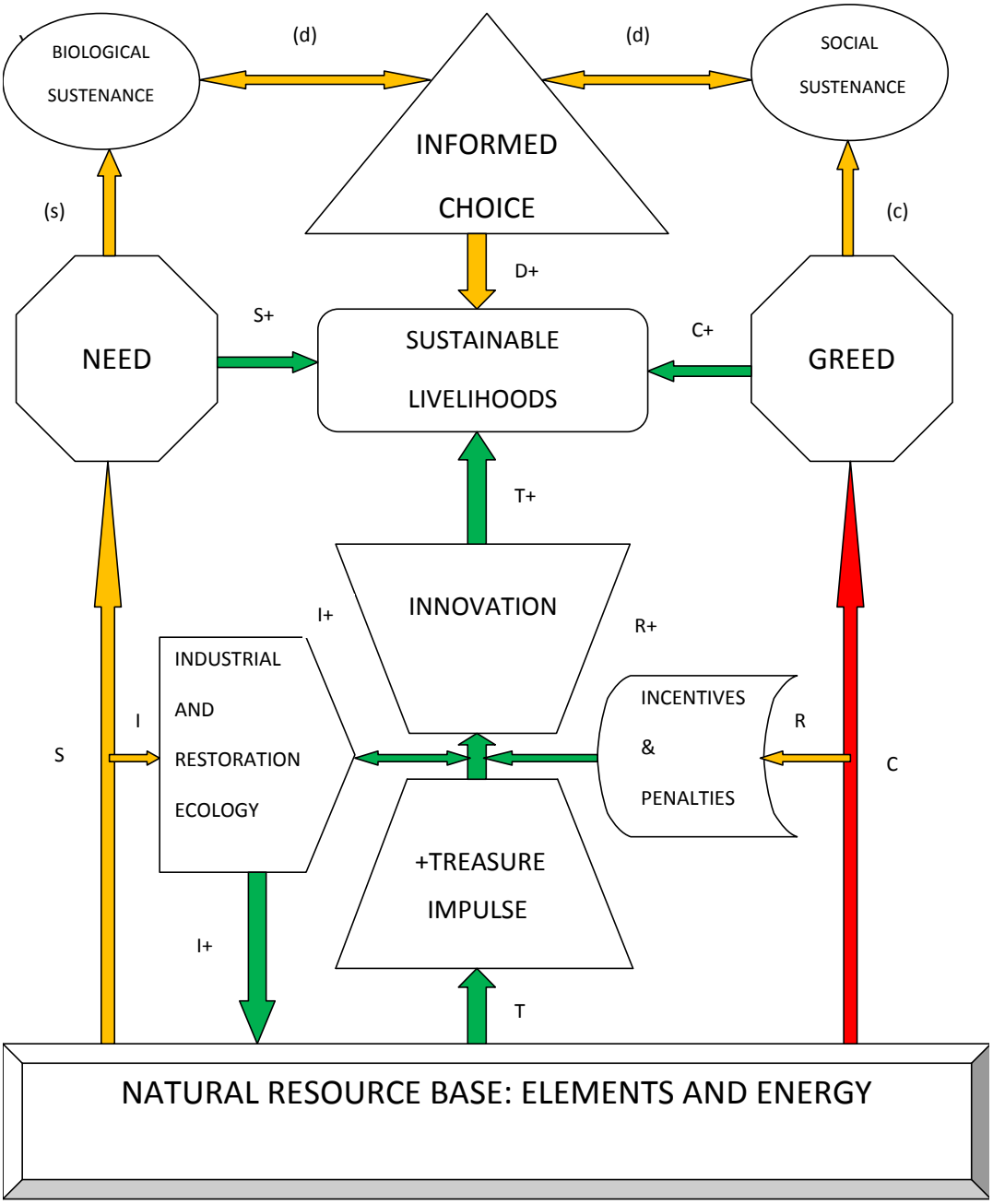
If there is a nefarious necessity in this whole debate, it is perhaps the specter of regulation. The common good of planetary protection will have a political price that pits proponents of individual liberty against the regulators. We need a new approach to govern economic development that would involve regulating the scale of consumption in developed countries, while creating incentives for constructive consumption and trade in developing countries for poverty alleviation. It's high time we have a more nuanced and "naturalized" approach to economic growth that acknowledges the resilience as well as the constraints of ecological systems.

Integrated view of a pluralistic sustainable society (Refer to Figure 1 on Page 4)

In my book *Treasures of the Earth: Need, Greed and a Sustainable Future* (Yale University Press, 2010), I tried to critique the insularity of minimalist tendencies of modern environmentalism that often neglect the opportunity costs of livelihoods in the developing world. For example, an environmentalist's call for reduction of consumption of luxury goods might not consider the impact of such a decision on a country like Botswana which has used diamond wealth for developing a fairly robust democratic economy.

As a follow-up to this book, I have tried to develop a framework for how to conceptualize the challenge of sustainability in a way that integrates livelihoods around human "need" (biophysical necessities) and "greed" (psychosocial attributes that contribute to the quality of life) which is show in Figure 1. Green arrows indicate positive pathway towards ecological, economic and social sustainability; red arrows define negative pathways for same criteria and yellow arrow defines pathways whose impact can be positive or negative depending on decisions nodes. S= Subsistence and survivalist demand; C =direct greed-based consumption (or plunder); R = Regulatory measures; I = Innovation Capital; T = Technologically driven demand; D = Democratic process. Lower-case notation suggests subsidiary pathway of concept in upper-case. + Indicates pathway with definite positive potential for sustainable development.

Figure 1: Livelihoods as the Natural Interface in a Sustainable Pluralistic Economy



Variables to be considered in Assessment tool for Development Planners

Research and analysis of multiple variables from the supply and demand sides would be needed to develop this tool and test its efficacy at an international level. Here are some the key variables that will be investigated in this regard. One or two key industrial sectors will be chosen as a pilot for the purposes of this proposal. The choice of that sector would be based on scoping data garnered through a workshop of experts convened at the start of the project. For each of these variables, a composite index may need to be developed which would be fed into the integrated planning framework. Some of the budget is allocated to reaching consensus among experts and decision-makers around the development of such indices for application.

Products and Services Demands Assessment: For a given industry, such as the automotive sector, consumer needs could be assessed based on secondary demand data. However, for measuring sustainability, it would be important to consider 3 scenarios for meeting demand and its impact on livelihoods: i) durable products with service sector employment (reusing old cars operating with employment for those who service them readily); ii) High turnover 'disposable' product with direct employment throughput; iii) Disposable product with technologically driven material recovery and reuse (Pathway T, Figure 1).

Natural Resource Base Inventory: Key ecological strengths within a governed jurisdiction that will be undertaking the planning exercise will be inventoried. Indicators to be developed include, mineral resource based, arable soil, energy availability from local renewable sources versus ease of importing energy.

Human Capital and Labor Availability: Demographic indicators of workforce composition and existing skill-set will be evaluated and a needs assessment for particular educational or skill deficits determined. A qualitative assessment of how such a deficit could be overcome would be included as a supplement to the analysis.

Existing Economic Profile and Infrastructure Indicator: The industrial capacity of the jurisdiction could be measured through available indices. What would be different from conventional measures of economic performance here would be an inclusion of an "opportunity" variable within the analysis, accounting for what range of development paths the economic profile of the country could reasonably afford.

Diversification potential: With the proposed development paths that emerge from the aforementioned evaluation criteria, a measure of diversification from capital flows generated by a particular sectoral development would be evaluated, under norms of governance that are prevalent. Instruments such as sovereign wealth funds could be an example of how such a metric could be calibrated.

Ecological and Social Evaluation for Development Paths using Industrial and Restoration Ecology Indicators: Once the integrated analysis of economic opportunities using the aforementioned criteria has been undertaken, techniques such as Life Cycle Analysis will be used to consider relative impacts of material usage choice for industrial development path as well as the resilience of the environment to industrial impact and the restoration potential.

Multiplier Effect of Employment for Development Path

Each development path will also be evaluated using conventional techniques of multiplier analysis to gauge the extent of employment potential. An additional metric of temporal stability of such employment will be added based on data for similar sectors or through appropriate models of projected employment based on projected changes in demand scenarios.

Two key deficit areas to be evaluated for policy analysis:

Demand is absent for goods and services that have most livelihood potential: Considering the development paths of particular economies with limited alternatives may suggest specific trajectories that are most viable from a sustainable livelihoods perspective but for which there is limited demand. An example in this regard is recent ongoing research by the author on the pearl farming sector in small-island states as a means of creating positive incentives for coral reef conservation. This sector may have high potential for sustainable livelihoods under the aforementioned framework but demand for South Sea pearls is highly limited to the Japanese market. In such cases the assessment tool would help to develop consumer education and policy interventions to assist in creating positive demand or vice versa.

Trade Needs Analysis

The Natural Resources inventory and related metrics may also lead us to note particular trade inputs for the success of a particular product. Trade linkages across the planet could be analyzed using tools from complex systems research to propose an optimal strategy that minimizes ecological impacts while providing maximum livelihood potential in areas with greatest need. Such an analysis has never been done from an industrial ecology perspective and could be revolutionary if applied to international trade governance.

Ultimate Goal

Once such an integrated tool has been developed with the requisite research and testing in specific jurisdictions within countries and internationally, the sustainable livelihoods assessment could become a new mechanism for trade and labor negotiations and international environmental policy. Currently there is a fracture between international organizations such as the World Trade Organization and environmental organizations such as the United Nations Environment Programme, which has very limited authority. A tool of this kind could provide a methodologically rigorous means of harmonizing these disparate organizations and giving them a common means of functional evaluation.

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Biography of applicant: Saleem H. Ali is Professor of Environmental Planning at the University of Vermont and a Fellow of the Gund Institute for Ecological Economics. His latest book is titled Treasures of the Earth: Need, Greed and a Sustainable future (Yale Univ Press, 2009). He was selected by the World Economic Forum as a "Young Global Leader" in 2011 and an "Emerging Explorer" by the National Geographic Society in 2010. Prior to embarking on his academic career Dr. Ali worked at General Electric and at Industrial Economics Inc. He received his doctorate in environmental planning from MIT, Masters in environmental studies from Yale University and Bachelors in Chemistry (summa cum laude) from Tufts University. Dr. Ali received his secondary schooling in Lahore Pakistan and is a citizen of both the United States and Pakistan.

Initial Budget Estimate for INET Proposal (based on a total 24 month grant)

Details of budget distribution over the 2 years will be worked out in consultation with INET as needed if proposal advances to Stage 2. However, it is estimated that this distribution will be divided evenly across both years of the grant.

Saleem H. Ali, University of Vermont, 2011

Category	Description	Estimated budget
Experts Group Workshop	An opportunity to convene a select group of experts through a cost-effective webinar/seminar to consider industrial sector for focus of proposal and vetting variables proposed for assessment framework	$5000
Data acquisition for Life Cycle Analysis	Acquiring data sets for material flows and	$10,000
Data Acquisition for Economic indicators	Some indicators data may be available free	$10,000
Graduate Student Support	Two-year support for a doctoral student would be matched with one year TA from the University	$40,000
Two month summer salary for PI	Devoting two clear month of time	$20,000
Project web site	Working with nonprofit web developer Tamarack media in Vermont, rapid dissemination of findings will be essential	$5,000
Publishers subsidy	University of Chicago Press has expressed a strong interest (providing a letter of support for this proposal as well) for a series of monographs emanating from this research	$5000
Conference presentations expense	Dissemination of the findings will be critically important as this project moves forward -- expenses for presentations at major international forums	$5000
University overhead 10% Maximum	The University of Vermont will absorb remaining overhead cost	$10,000
TOTAL		$110,000

From: Phillip A. Sharp
Sent: Sunday, October 16, 2011 8:49 PM
To: bioeconomy@ostp.gov
Cc: Margarita Siafaca
Subject: Comments on National Bioeconomy Blueprint

Dear Madam/Sir,

I strong endorse the National Bioeconomy Blueprint recently announced by the administration of President Obama. The investment in development of new technologies and science to further improvements in food production, sustainable energy, the environment and healthcare through innovation will yield multiple returns for the country including new jobs, and a better quality of life. These initiatives are possible due to breakthroughs in life science over the past decades. Developing programs that integrate engineers, physical scientists, and computation scientists into life sciences are critical for progress as these real world problems are surmounted. I look forward to amazing results from this new initiative.

Sincerely yours,

Phillip A. Sharp

From: Kory R. Johnson, MS, Ph.D.
Sent: Monday, October 17, 2011 4:49 PM
To: bioeconomy@ostp.gov
Subject: My Suggestion ...

Hello,

Thank you in advance for considering my suggestion.

My suggestion relates to research grant funding for small businesses. Specifically, grant funding requirements thwart innovative ideas that can lead to global health changes and marked improvement by making funding available per grant too low.

If I have an idea to cure cancer and would like to pursue it, yet the grant offers not enough money to allow me to quit my job and give a go at doing so. Well, I don't quit my job and I don't give a go. Leaving what could be the greatest idea ever an idea with no hope of being recognized.

Now, I have such ideas and am ready to give a go. But, alas funding requires me to keep the idea a dream. How many others ideas have been lost that could have been recognized because grant funding is too low.

Making more money available per grant to support the payroll for researchers would bring tidal wave of new and amazing ideas that would change the world. My recommendation, change strategy to stop financing many small ideas to be worked on part-time. Rather, financially back potential block busters that can be worked on by those who have the know how and the skills. But again, do not even attempt nor contemplate due to the amount of money not being able to compete with what a full-time job provides.

Best,

Kory R. Johnson, MS, Ph.D.
/www.koryrjohnson.com/

From: David Johnson
Sent: Tuesday, October 18, 2011 1:45 AM
To: BIOECONOMY@OSTP.GOV
Subject: Bioeconomy input

Dear federal official:

I am founder, President, and CEO of a small biotech company in San Francisco. We are using our innovative technology to characterize disease using rare cells circulating in the blood. The first application is in immunology. Our tools for immunology are like a "CT scan" for the immune system, providing unprecedented portraits of immune response to disease and disease therapy. We will address big problems in cancer, infectious disease, and transplantation. All of my 10 employees have a PhD or MD, and make over $80,000. I've hired all 10 in 2011. We are funded with $600,000 in federal grants and $410,000 in venture capital. This is my second company, and I'm only 35. I can tell you a lot about innovation and what works.

I want to answer your questions directly:

(1) Translate next-gen sequencing into clinically relevant applications. My technology is doing this already, but, VCs often get more excited about funding technology rather than clinical applications, so next-gen sequencing and other novel technology is getting stuck in University labs without much impact on patients. Recently I had an acquaintance ask me about sequencing their tumor. There are many interesting things to glean from sequencing a tumor, but it takes 10-12 weeks to do the sequencing. So, you may have a $1k genome, but it doesn't matter if it takes 10-12 weeks, because your patient is dead. Thus -- a disconnect between University and reality. In general, I would work to support private industry more than Universities. It just doesn't make sense that SBIR is only 2.5% of the extramural NIH budget.

(2) Move money away from Universities and towards funding small, innovative companies that want to move their inventions to market. Biotech companies are expensive to start, but they drive innovation for the entire industry. At least force Universities to publish open source so that all citizens can benefit from their research without paying tremendous fees to closed-source journals.

(3) There are hardly any technical challenges that high-throughput methods haven't already solved. The problem is getting the technologies to clinical market. Reform and consistency in the FDA, clearer guidance in CLIA, and more consistent regulations among states would bring the methods to clinical market. Is it too much to ask to have consistency between administrations?

(4) You could fund my company to get these data. This is exactly what we're doing, but we're struggling to get enough capital to get our products to market. Multidisciplinary sounds like a big University consortium, which would be a tremendous vortex of wasted money. Most University research goes nowhere and gets filed in a closed-source academic publication at best.

(5) Move money from academic research to companies. Companies bring research to clinics.

What's the incentive for an academic to do this? I recommend more "matching" grants, i.e., the federal government provides money only if a VC matches the funding. VCs are sitting on a lot of money and need incentives to loosen their purses, especially for early stage investments. Also, you could somehow provide more incentive to get Universities to license their technologies. I've tried many times to license technologies from Stanford, and they were very conservative. Most inventions die in Stanford's tech transfer office, never to see commercialization. Remember also that most, if not all, of these inventions were possible only with federal grants, so Universities are in effect sitting on taxpayers' inventions.

(6) There has been a lot of commotion in Congress to change SBIR, but it's an awful, awful idea. This is just another case of well-funded special interests hijacking an excellent program. SBIR is probably the single most effective program in the federal government in terms of job creation. NSF officials told me that companies funded at NSF's SBIR program generate $7 in tax revenue for every $1 invested. How can you beat that? Just don't change SBIR! If you do anything, increase the percentage of the budget allocated to the program.

(7) It would be interesting to get clinical data from VA patients, ideally associated with some kind of genetic information. I know, this is highly unlikely, but a major hurdle in getting clinical genetics in motion is the phenotype data associated with the genetic data. Genetics is no longer the bottleneck. More open repositories for tissue samples would also be helpful.

(8) VC is suffering from the global economic malaise. They are becoming conservative just like everyone else -- how can you blame them? I spend a lot of time in China, and they spend a lot of time on 5- and 10-year plans. There is long term planning there, and long term stability. American business doesn't want to grow in part because they can't seem to get a handle on political uncertainty. How can you plan a business when you're getting massive stimulus giveaways one year and then spending cuts the next year? My concrete suggestion is to work harder to create stability in the government. Tax, spend, cut, regulate -- whatever, just make it consistent.

(9) I could go on and on about this. For one thing, any PhD student who gets federal funding should be *required* to do internships in the private sector. Currently, it's nearly impossible to get your department to let you take these internships. Why would they let students do this, when they're such cheap labor? The only way to make it happen would be for the feds to force them into it. This would make students better prepared for the real world, and also help them to understand what they want to do with their lives. I would also encourage more hybrid programs, such as bio-IP, bio-entrepreneurship, bio-operations, etc., which give students more breadth rather than just scientific knowledge.

(10) I have no openings for graduates of community college, and can't imagine that I ever will.

(11) Because Universities fail to provide practical knowledge, I'm forced to spend a lot of time training staff. I consider this a cost of doing business and take pleasure in mentorship, as long as the employee is motivate. I'm open to internships, but it's often difficult to find students who can take time off from their labwork.

(12) Government could preserve the SBIR and STTR programs, or grow them if possible. Government (especially local government) could work to develop more incubator spaces for small companies. San Francisco is leading the way on this with the biotech cluster near UCSF (QB3). Landlords have little incentive to rent to small companies, but small companies need specialized lab facilities. QB3 makes all that happen. These should be near Universities all around the country. Industry is entrepreneurship, so they could keep doing what they're doing. Universities could reform their tech transfer departments, which, by the way, sit on inventions funded mostly by the federal government.

(13) The FDA has issued few clear guidelines for IVD-MIA. VCs often cite this as a reason for not funding companies in the genetics field. It's often not clear which tests would fall under IVD-MIA, and which would be considered homebrew and regulated by CLIA. Again, consistency and clarity in regulations are very important.

(14) ibid

(15) FDA seems poorly equipped for tests that involve next-gen sequencing data. Because no tests have been approved, it's difficult to point to a specific example. None of my colleagues have even tried. We tend to go for CLIA, even if FDA might consider that test an IVD-MIA.

(16) I would never pursue public-private partnership because of government's general inconsistency between administrations.

(17) ibid

Thanks for taking comments.

Kind regards
Dave

--
David Johnson, PhD
Founder and CEO
GigaGen, Inc.

From: Dennis Miller
Sent: Tuesday, October 18, 2011 1:42 PM
To: 'bioeconomy@ostp.gov'
Subject: building a 21st century Bioeconomy

TO: Mary Maxon and Mike Stebbins:

I think the attachment covers most of the points you listed in your request for ideas and assistance in regard to "Building a 21st Century Bioeconomy." This attachment was prepared with the support of our partners Arcadis and Solena Q. Please let me know your questions.

With best regards,

Dennis F. Miller
Vice President & Science Advisor
Solena Group, Inc.

About Solena Fuels,

Solena Fuels (Solena) is a next generation zero emission bioenergy company that has developed integrated end-to-end solutions that would help satisfy the world's growing energy demands while reducing the greenhouse gas emissions and high expense normally associated with the usage of fossil fuel-based energy. Solena's suite of integrated solutions includes patented plasma gasification technology that is Six Sigma optimized after more than ten years of development, an integrated plasma gasification combined cycle process, and a CO_2 capture-to-algae growth and harvesting system.

Using its proprietary technology, Solena Fuels has developed a synthetic fuels solution and business model that addresses the historical challenges faced by the biofuels market. Solena Fuels' synthetic fuel is a "drop-in" fuel that allows airlines and shipping companies to utilize a sustainable energy source without any changes to their engines or infrastructure. This proprietary technology allows Solena to use a wide variety of heterogeneous waste feedstocks that do not compete with crops or use water. We partner with the end users of our fuel to develop a facility that allows them to sustainably operate their business.

Solena Q NRG is a joint venture between ABSi Corporation and the Solena Group focused on developing renewable energy solutions for the United States Public Sector market. Formed to harness the energy contained in biomass and other organic wastes to produce power and bio-fuels in a clean, responsible and renewable way that preserves the environment, empowers America's communities, provides green jobs and increases energy security in the United States, Solena Q will lead the development of projects deploying Solena's next generation plasma gasification technologies. Solena Q NRG is the second joint venture between ABSi Corporation and the Solena Group. Solena-ABSi India Private Limited (SAIP) was established in 2008 to bring clean energy from organic waste materials to the communities of India. Projects are under development in New Delhi, rural India and Sri Lanka. ABSi Corporation is headquartered in Rockville, MD and provides technology services and energy solutions, helping both government and commercial organizations achieve technology goals and business objectives. ABSi's domain focus comprises large-scale enterprise computing, healthcare IT and cyber-security, and renewable energy.

About ARCADIS

In 2009, Malcolm Pirnie, Inc. merged with ARCADIS U.S., Inc. ARCADIS is an international company providing consultancy, design, engineering and management services in infrastructure, water, environment and buildings. We enhance mobility, sustainability and quality of life by creating

balance in the built and natural environments. ARCADIS develops, designs, implements, maintains and operates projects for companies and governments. With 16,000 employees and more than $2.7 billion in revenues, the company has an extensive international network supported by strong local market positions. ARCADIS supports UN-HABITAT with knowledge and expertise to improve the quality of life in rapidly growing cities around the world. Visit us at: www.arcadis-us.com ARCADIS has extensive Federal experience and has been working for the Department of Defense (DOD) since World War II, when the entire firm was dedicated to the build-up in support of the war effort. We have successfully managed task order assignments in excess of $500M involving over 20 Corps Districts during the last 10 years and completing projects at over 350 Army installations including numerous OCONUS locations. All of ARCADIS' ACASS ratings are satisfactory with 88% recorded as "Outstanding" or "Very Good". Arcadis is also currently undertaking several high-profile Federal assignments that include work for the DLA's Energy division (former Defense Energy Supply Center) on a multi-million dollar technology study to develop deployable alternative fuels solutions to reduce current DOD's petroleum consumption and maximize alternative fuel sources. Similarly, for the DOE's National Renewable Energy Lab (NREL) R&D program, they are evaluating alternative and renewable energy technologies for application across a wide infrastructure, including cutting-edge uses of solar, wind, biomass and geothermal systems.

1. Current and future production capabilities, including pilot-scale capability.

Solena Fuels is developing several next generation, patented Solena Plasma Gasification and Vitrification (SPGV) Biomass to Liquid ("BTL") biofuel plants or Integrated Biorefineries within the United States, Europe, South America and Australia. All Solena biofuel projects are privately financed, but seek Federal Loan Guarantees when available. Each plant requires 24 months to construct. Over that period, approximately 1500 construction workers will be hired. The permanent staff is approximately 175.

Solena Fuels' BTL facilities are designed to process approximately 592,000 tons annually of a biomass waste or Refuse Derived Fuel (RDF) to generate 25 million gallons per year ("mmgy") of sustainable aviation fuel or FT diesel for marine use and bionaphtha as well as 33 MW net of baseload renewable electricity, which can be exported to the grid. Of the 25 million gallons, 16 million gallons are FT bio-jet fuel or FT diesel and 9 million gallons are bio-naphtha, which can be used for a variety of applications in the biochemical and petrochemical industries.

In the United States, two BTL plants are in advanced stages of development. The first of these BTL plants, to be sited in Gilroy, CA, which has the aforementioned throughput and production capacity. This project is tied to the project development efforts spearheaded by Solena, which led, in July 2011, to Solena signing a Letter of Intent (LOI) with ten leading air carriers, including (i) eight members of the Air Transport Association of America (ATA): United Airlines (UA), American Airlines (AA), Federal Express (FX), Air Canada (AC), Southwest Airlines (WN), Alaska Airlines (AS), JetBlue Airways (B6) and US Airways (US); (ii) Lufthansa; and (iii) Frontier Airlines. This LOI sets forth the air carriers' intention to purchase all the sustainable aviation fuel produced by Solena's BTL facility, which the airlines can use at the San Francisco, San Jose, and Oakland airports. A second project, located in a large Midwestern city, has been under development by Solena for two years. Midwest project partners include General Electric, the local utility (which is a public charitable trust), Arcadis and other

highly reputable American technology and equipment supplier conglomerates. The project is slated to be one of the largest clean energy biomass and biosteam facilities in the United States and will be announced in the fall of 2011. A third project involving a Solena BTL plant in the US northeast is in discussions for the production of sustainable FT diesel for a leading global shipping company.

Internationally, BTL projects are being developed in Europe, Australia, South America and India. Most notably, Solena has an agreement with British Airways for the development of Europe's first bio-jet fuel plan that will produce, as above, 25 mmgy of sustainable FT biofuels and 33 MW of exportable baseload electricity. British Airways has committed to be an investor in this project. The British Airways BTL facility is scheduled to commence construction in 2012 and will be commissioned in 2014. In Australia, Qantas Airways Limited has partnered with Solena to build a similar BTL plant to convert RDF into bio-jet fuel. A third plant is being planned in a large central European city with one of Europe's most important air carriers. Additional discussions underway in Asia include other major Asian airline companies.

In addition to FT bio-jet fuel, the Solena Fuels business model also includes production of sustainable FT marine diesel. As such, Solena is in discussions with a major global shipper to provide FT diesel from BTL or Integrated Biorefinery plants that would be produced at or near ports in the United States, South America and Africa. Solena also is confident that sustainable FT marine diesel produced from locally sourced RDF and with net zero CO_2 emissions will enhance US energy security and have great appeal to the U.S. Navy as it plans to field a carrier strike group powered by biofuel by 2016 and moves toward supplying half of its energy needs with renewable sources by 2020.

Pilot scale capability

The core and distinct element of Solena's Biomass to Liquid (BTL) solution is the Solena Plasma Gasification and Vitrification (SPGV) reactor, operating on any type of biomass including waste. In addition Solena's strategic BTL solution partners include a world-leading, US-based FT technology provider, and a highly reputable and experienced FT product upgrading and refining conglomerate.

More than 10 years of developing, pilot testing and refining the SPGV technology and solutions have allowed Solena's team to collect, compile and analyze a significant amount of material and operating data. The Company has used this data to design, develop and patent its proprietary solutions including its steady state gasification computer model in order to simulate system performance and design control systems to regulate and monitor each BioEnergy Plant. Solena's technical team has been continuously extending its know-how and intellectual property through a strong R&D strategy. Solena gained experience in gasification by means of two pilot facilities. Solena's patents are based on the knowledge developed during tests campaigns at these facilities.

Raleigh, North Carolina Test Facility

Solena first tested several types of materials in 1996 at a test facility at Research Triangle Park, North Carolina. Tests performed at this facility showed a very high specific energy

requirement (SER) of about 1,000 kWh per ton of waste treated. This phenomenon was due to the fact that all of the plasma energy contained in the plasma jet was directly pointed to the waste. Consequently, in order to break down the chemical bonds of the waste, physical elements of waste had to be in direct contact with the plasma jet to properly gasify it. These tests and/or treatment periods were performed on behalf of clients (public or private) and in conjunction with research and development efforts. Several feedstock streams were treated and gasified by the plasma systems, which will be outlined in section 2.5.

Madison, PA Pilot Plant Facility

In conjunction with the Westinghouse Plasma Center, Solena validated a revolutionary process to enhance its gasification efficiency, in terms of syngas composition and energy efficiency. This R&D effort resulted in a new gasification process and reactor design. The testing was conducted in 2000 at the former Westinghouse demonstration facility located near Madison, PA in 2000. As a result of this research, specific equipment was used in the gasifer for uniform distribution of the plasma heat across the gasifier's cross-section. Operating parameters such as plasma power, biomass feed rate, enriched-air feed rate, and others have been optimized, resulting in an optimized syngas composition, suitable for numerous industrial applications and lower costs of operation. Equally important, process flow rates were large enough to provide reliable scale-up for commercial plants.

Commercial Testing and Other Relevant Pilots

A key result of Solena's pilots and subsequent computer modeling was establishing and documenting the high quality and stability of the bio-syngas produced by Solena's patented SPGV process. Working with its strategic technology partners, Solena's BioSynGas has been determined to be a suitable feed for the FT process. Solena's Fischer-Tropsch partner currently operates a demonstration facility in the US producing 400 gallons per day of certified Synthetic Paraffinic Kerosene ("SPK") that has been certified to meet ASTM D7566 standard specifications for aviation fuels as a 50/50 blend with fossil-based jet fuel.

Siting: Rationale on where such facilities could be best sited

Currently, Solena and its U.S. public sector development partner, Solena Q, is targeting locations near high-traffic airports with airlines that will purchase the bio-jet fuel off-take, large municipalities, strategically located rural locations, and military facilities and installations that have already benefitted, or stand to benefit from, the Base Realignment and Closure (BRAC) process. From discussions with the Defense Logistics Agency (DLA), Solena understands that minimizing fuel transportation costs is a priority, thus making proximity to major airports, pipelines that can transport bio-jet fuel, refineries and military installations, important strategic business considerations.

Since Solena's plants are feedstock flexible and predominantly use waste products as well as other agricultural material, they are not limited in location as other biomass plants that rely on a specific type of feedstock may be. Solena is undertaking projects in locations where there is a combination of local demand, well-developed community relationships, value-adding business partners and commercial entities that will purchase the biofuel products along with

municipalities, rural jurisdictions and military installations. Solena is in active discussions with local authorities in Hawaii to implement a strategic bio-fuel project and has had some discussions with the U.S. Navy at Pearl Harbor.

2. **Future plans to build/expand/retrofit, including ability to finance, a rationale on where such facilities could be best sited, and identification of the major biomass feedstocks that could be employed**

As previously indicated, Solena has signed letters of intent/memorandum of understanding for 11 Solena BTL plants. Additional plants in the United States beyond the Gilroy, CA and Midwest projects are also envisioned for both military and commercial customers and municipalities and rural areas. (Please see discussion below of State and Local Policies and Incentives). The Midwest project would involve retrofitting existing infrastructure for the production of steam for industrial customers. Rural-based Solena BTL plants would require both a long-term supply of waste biomass or RDF and/or agricultural waste feedstock and 15 to 18 acres of land for the same period. Solena is also open to the possibility of siting a facility at a military base under an Enhanced Use Lease arrangement.

The ability to finance any of the referenced Solena projects in development and any future projects (whether as a new build or a retrofit), ultimately depends on whether an economically acceptable, long-term feedstock supply agreement, offtake fuels agreement and power purchase agreement can be secured. Solena currently seeks to enter into long-term contracts of at least 10 years to ensure bankability of the projects. Solena is confident that, based on its current economic modeling and plant design, it can offer highly competitive pricing for its green and sustainable outputs, independent of spot price volatility.

Currently, Solena and its US government development partner, Solena Q, is targeting locations near high-traffic airports with airlines that will purchase the bio-jet fuel off-take, large municipalities, strategically located rural locations, and military facilities and installations that have already benefitted, or stand to benefit from, the Base Realignment and Closure (BRAC) process. From discussions with the Defense Logistics Agency (DLA), Solena understands that minimizing fuel transportation costs is a priority, thus making proximity to major airports, pipelines that can transport bio-jet fuel, refineries and military installations, important strategic business considerations.

The feedstock streams that can be used for the Solena process include:

- Biomass;
- Municipal solid waste;
- Out-of-use tires;
- Hospital waste;
- Landfill material;
- Agricultural waste
- Industrial waste
- Mixed source biomass and waste (different biomass sources with MSW, tires, etc.)

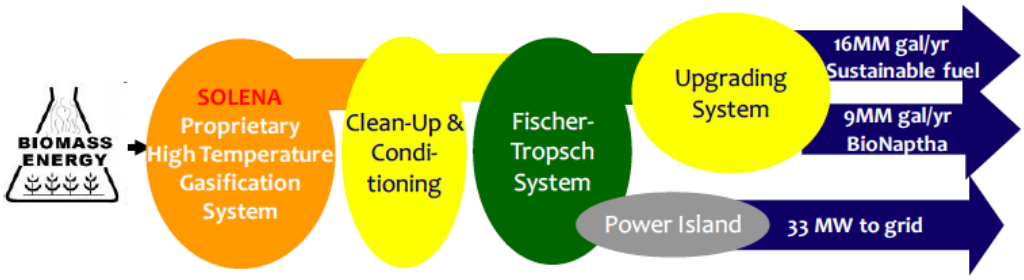
3. **General description of your conversion technology, a description of your existing or contemplated end-to-end supply chain, any partnerships contemplated or required to**

obtain feedstocks and plans for moving forward to establish relationships to assure sufficient feedstock supply, plans for the blending of the biofuel component with conventional petroleum products, and plans to provide final delivery of blended fuels.

Technology Description

Solena's BTL solution consists of five integrated processing "islands": (i) Solena's proprietary high-temperature gasification; (ii) a BioSynGas conditioning island; (iii) a Fischer-Tropsch ("FT") processing island; (iv) a FT wax upgrading island; and (v) a power production block.

Each of the processing islands comprising the BTL Facility are illustrated in the figure below and described hereunder.



The BTL facilities are designed to process 592,000 metricTons/year of biomass feedstock to produce (i) sixteen million gallons of sustainable aviation or marine fuel; (ii) nine million gallons of sustainable naphtha; and (iii) 33 MW of baseload electricity that are exported/sold to the grid.

Solena Proprietary High Temperature Gasification Island

The first processing block in Solena's BTL solution is its proprietary high temperature gasification system. This processing block converts the solid biomass feedstock into a combustible gas fuel called BioSynGas. In order to achieve this, the feedstock is fed into Solena's proprietary gasification vessels ("SPGV") where it is subjected to extremely high temperatures. The SPGV vessels are plasma-enhanced counter-current fixed bed gasifiers. These high temperatures are generated by a plasma heating system, which is one key features of Solena's gasification process. Another key aspect of Solena's proprietary gasification process is the use of a catalytic bed, which distributes the heat from the plasma torches evenly and is the reason for the stable operation and lower power consumption of the system. The result of applying the high temperatures to the solid feedstock is that the solid organic matter (i.e. wood, paper, plastics, food, etc.) depolymerizes into its most elemental atoms, which then recombine to form the BioSynGas. At the same time, the inert materials such as metals that may be entrained in the feedstock and the inert fraction of the feedstock melt under the high temperatures and exit the SPGV as molten lava, which after cooling becomes an inert basaltic rock called "slag". This slag, which is five times less leachable than bottle glass and comprises less than 7 percent of output, can be safely used as construction material with numerous commercial applications (e.g., road fill, concrete mix, bricks, tiles, etc.).

This process is also known as “thermal de-polymerization of organic materials and melting of inorganic materials by means of high temperature plasma energy” and is Solena’s patented gasification system.

As the conversion of any carbon-based material is in excess of 99%, the efficiency of these systems is very high. This is a particular benefit of the SPGV process: a highly cost-effective and technically efficient thermal de-polymerization process.

BioSynGas Conditioning Island

Upon exiting the Gasification Island, the raw BioSynGas is sent to the BioSynGas Conditioning Island. Although the raw BioSynGas is free of tar, soot, dioxins and furans, it does contain moisture and acid compounds that can be recovered, ensuring the BioSynGas meets the specifications of the Fischer-Tropsch system. The conditioning process is carried out in several steps in the BioSynGas Conditioning Island. The first step consists on lowering the temperature of the raw BioSynGas by quenching it with water, which makes the BioSynGas more manageable and less corrosive to the downstream equipments. Then, any remaining heat in the gas is recovered and used to generate steam, which is later used to produce additional power in the Power Production Block. Once the BioSynGas has been sufficiently cooled, its acid components are scrubbed off. This is done using off-the-shelf scrubbers vessels that essentially ‘shower’ the gas with process water and / or a solution to remove and recover the acid compounds. Finally, the moisture accumulated in the BioSynGas is removed using a series of filters and moisture separators. At this point, the BioSynGas is free of all pollutants, moisture and acid compounds and is also known as ‘sweet & dry’ BioSynGas. The conditioned sweet & dry BioSynGas meeting all required specifications is then sent to the Fischer-Tropsch processing Island.

Fischer-Tropsch Processing Island

The Fischer-Tropsch process is a chemical synthesis that consists on converting the BioSynGas into liquid fuels. The process is named after the German scientists who invented it in the late 1920’s and was used during World War II in Germany to produce substitute fuels. The FT chemical synthesis consists on passing the BioSynGas through a bed packed with a specially formulated catalyst within what is called the Fischer-Tropsch reactor (FT reactor). Inside the FT reactor, the catalyst helps drive a chemical reaction that synthesizes the gas into a heavy wax product and light Fischer-Tropsch liquids or LFTL, referred as FT products. In essence, the FT products can be considered a sustainable, sulfur-free version of conventional crude, and they are then sent to the Upgrading Island for further processing. The FT Processing Island also produces a tail gas that is a combustible fuel suitable for driving gas turbines in combined cycle. As such, and as described later, the FT tail gas is used within the BTL facility for power generation.

FT Products Upgrading Island

The FT products Upgrading Island receives the heavy wax product and LFTL generated in the FT Processing Island and refines them into the finished sustainable liquid fuels. This upgrading process, which is similar to the process that takes place in a conventional refinery, is

the step that ultimately yields the two main products from the BTL plant: sustainable BioJetFuel and BioNaphtha.

Power Production Block

As mentioned above, the FT Processing Island also produces a combustible tail gas that is suitable for driving gas turbines and therefore this FT tail gas is used in the Power Production Block within the BTL facility for power generation. The Power Production Block consists on gas turbines in combined cycle, which means that after the tail gas fuel has been combusted in the gas turbine, the heat produced in the combustion is used to generate additional steam. This steam, together with the steam produced in the FT Processing Island and the steam produced in the BioSynGas Conditioning Island, is then used to drive a steam turbine for generating additional electrical energy. This way, the combined cycle maximizes the power production and energy recovery efficiency of the plant. Finally, after recovering the heat energy from the exhaust of the gas turbine, the exhaust is released to the atmosphere via the Continuous Emissions Monitoring System (CEMS) as standard industry practice to ensure that applicable emissions standards are met. In all cases, the emissions from the turbine exhaust gases are in fact lower than emissions from a natural gas fired plant.

The Solena BTL plants are far cleaner and more efficient than current waste-to-energy mass burn plants in operation. The BTL facilities produce near net zero carbon emissions, no toxic ash, bottom ash or fly ash, and minimal emissions of SO_x, NO_x and particulate matter. The plants substantially reduce carbon dioxide emissions by reutilizing waste that would otherwise be sent to landfills, which generates emissions of greenhouse gases as well as other harmful environmental affects. The bio-jet fuel presents an estimated life-cycle greenhouse gas (GHG) emissions savings of 95% compared to the fossil-based jet fuel currently used by the airlines. The plants also create approximately 1,200 new jobs during construction and 175 permanent jobs during the life of the plant. Solena biofuels are cost competitive with petroleum-based fuels and meet ASTM D7566 Standard specifications for use as a 50/50 drop-in fuel by the United States Air Force and commercial airlines. In addition, the FT diesel produced may also be used by global shipping freighters to abide by increasing sulfur oxides emissions restrictions. The Air Force can utilize American-made Solena bio-jet fuel to move toward its goal to have half of its domestic fuel needs drawn from alternative sources by 2016.

Description of Solena's existing or contemplated end-to-end supply chain

The chain of activities leading to the production and delivery of biofuels to the end customer starts with the sourcing of the feedstock material. As indicated above, Solena has established relationships with highly reputable domestic and global waste management groups and negotiated Letters of Intent from three major feedstock suppliers for the supply of the necessary biomass waste. Prior to start of construction of a BTL project, Solena will engage in long-term feedstock supply agreements for the delivery of the necessary biomass waste to the BTL facility.

At the back end of the production facility, Solena anticipates the biofuels produced shall be picked up from the premises by the off-taker, who will then blend it with conventional fossil fuel to their required specifications.

Partnerships contemplated or required to obtain feedstocks and plans for moving forward to establish relationships to assure sufficient feedstock supply

In order to secure feedstock Solena has established relationships with reputable national waste aggregating entities and other global waste management companies. In addition, Solena also solicited and negotiated Letters of Intent from three other major feedstock suppliers in the US for the domestic BTL projects. As project development activities progress, Solena will seek to enter into long-term feedstock supply agreements with one or several such entities to guarantee enough feedstock is supplied to the BTL facilities.

One of the greatest advantages to Solena's facilities is that its process is feedstock flexible. The solution adds value to materials that would otherwise be landfilled. Any carbonaceous waste can be used as a feedstock, including municipal solid waste, agricultural and industrial waste. The United States Environmental Protection Agency (EPA) estimates that the average per capita municipal solid waste generation in the U.S. is 4.34 pounds per day. Municipal solid waste is abundant and ubiquitous in most large urban areas, military installations and municipalities in rural areas. Unlike many biomass sources, the infrastructure and systems to collect and delivery the feedstock to a central location is already in place and is a unique aspect of our business model. Solena's solution provides a clean, economical, and efficient alternative to landfills or incinerators in a time when more advanced solid waste management practices are a priority for many communities.

Since Solena's plants are feedstock flexible and predominantly use waste products, they are not limited in location as other biomass plants that rely on a specific type of feedstock may be. Solena is undertaking projects in locations where there is a combination of local demand, well-developed community relationships, value-adding business partners and commercial entities that will purchase the biofuel products along with municipalities, rural jurisdictions and military installations.

Regardless of the type of biomass sources used, there is very minimal negative impact on the environment. Under a US Environmental Protection Agency (EPA) definition, Solena's process is distinct from incineration and thermal waste disposal facilities. Compared to conventional coal-fired and other fossil fuel power plants, Solena's plasma gasification solution produces no air pollutants such as Semi-Volatile Organic Compounds, including dioxins or furans, or any toxic fumes, heavy metals, hazardous ashes, bottom ash, fly ash, or flue gas, as do incinerators or boilers. Solena's technology is a viable, cost-effective way to meet today's rigorous permitting regulations and to reap the environmental, societal and economic benefits of combating global climate change.

Plans for the blending of the biofuel component with conventional petroleum products, and plans to provide final delivery of blended fuels...

Please refer to sections 11 and 12 below.

4. Description of all value-added co-products resulting from the processing and conversion processes that have the potential to provide economic benefits and impact

the overall business case. Identify risks associated with producing, marketing and delivering value-added co-products and methods for mitigation.

Solena's BTL plants produce bio-syngas that is converted into bio-jet fuel or FT diesel as their primary product, depending on the requirement of the customer. In addition to the biofuels, several value-added co-products are produced as a result of the process. The BTL plants currently under development will export 33 MW (net) of clean, renewable electricity. The electricity can be purchased by the military installation, a commercial entity or the surrounding municipalities or rural areas.

Each BTL plant also produces nine million gallons of bio-naphtha annually, which may be converted to either power or more biojet or FTDiesel fuel. The bio-naphtha is highly marketable as it can be used as a solvent in paints and coatings by the chemical industry or upgraded into gasoline. It is also a valuable product in the petrochemical, mining industries, or petroleum industries. The bio-naphtha also has a high paraffin content, which makes it an ideal material for producing ethylene.

In addition, metals that are fed into the gasifier generate another co-product, inert vitrified slag. This has been approved by U.S. EPA as inert, and can be safely used as construction material. This slag would also be processed by Solena through commercial reuse channels where it will be used in a variety of construction products, including as construction aggregate for concrete or roadbed, construction fill material, brick making, architectural tile or shingle manufacturing.

Finally, the sulfur contained in the biomass feedstock is extracted from the BioSynGas during the clean-up and conditioning process in the form of sulfuric acid or pure sulfur cake, depending on local demand for this chemical co-product. Sulfur compounds have applications ranging from vulcanization of natural or synthetic rubber to the production of black gunpowder, insecticides, pharmaceutical products and disinfectants.

Solena anticipates that the slag and sulfur co-products will have negligible impact on the economics of the project or its business plan.

The greatest risk associated with the value-added co-products is a potential lack of a viable purchaser for the total amount of bio-naphtha that is produced. While bio-naphtha has a variety of uses, which are outlined above, purchasers of bio-naphtha may not enter into long-term purchase contracts. Bio-naphtha is purchased on a spot market so it is possible that when demand decreases, there will be excess bio-naphtha. Solena's mitigation strategy is to enter into partnerships with companies that utilize bio-naphtha and identify companies that need bio-naphtha before the plant is operational so there will be alternative purchasers of bio-naphtha.

5. **Estimated time from project inception to plant startup, including breakdown of time allowed for permit approvals, preliminary engineering, detail design and engineering, construction, commissioning, production startup and operations.**

The estimated timeframe from project inception to commercial operations is 30 months, including initial project development activities, permitting process, engineering, procurement, construction and commissioning of the facility.

Please refer to the preliminary milestone schedule enclosed at the end of this document for more details.

6. **Recognizing that fifty percent (1:1) is the minimum level of industry cost sharing that the Government will entertain, identify the total public-private investment required to undertake development and construction of a commercial-scale integrated biorefinery that meets the stated minimum capacity objective**

According to current modeling and engineering design work performed, the total cost to construct and commission the advanced biorefinery as described is approximately $350 million. This cost includes the projected pre-financial close and predevelopment cost of (i) Front-End Engineering and Design; (ii) land; (iii) contingency; (iv) total EPC cost to procure, construct and deliver a turn-key biorefinery plant with production parameters stated below; (v) closing/financing costs, including capitalized interest during construction; and (vi) wrap insurance costs.

7. **Estimated start-up costs to begin production of biomass-derived jet and marine diesel fuels that meet or exceed the targeted scale of production**

In order to begin production on a commercial scale, the amounts set forth in the cost and finance section above would need to be invested and deployed for construction and commissioning of the proposed biorefinery.

8. **Estimated cost per gallon of producing and delivering 50:50 blended biofuel, compared to that of petroleum-based fuel, over the first five year period of production**

Solena respectfully declines to provide an answer to this question at this particular time, as it is sensitive, competitive and confidential information. However, understanding the current cost of aviation and maritime diesel fuels, Solena believes that its cost to produce and ultimately the price of Solena fuels to its customers will be highly competitive to petroleum-based and other proposed green and sustainable biofuels solutions. Equally important, the sale price of biofuels under the bilateral off-take agreement will be independent of oil price fluctuations, which is a highly attractive attribute to prospective customers.

9. **Recognizing that a drop-in replacement fuel requires no change in systems configuration, engine architecture, fuel infrastructure, or fuel handling, document ability to meet anticipated product quality specifications as understood at this time, describe the fuel certification, and identify any issues or concerns.**

A 50/50 blend of Synthetic Paraffinic Kerosene ("SPK") to be produced by Solena's planned BTL facilities with conventional fossil-based jet fuel has already been certified to meet ASTM D7566 09 Standard Specification for Aviation Turbine Fuel Containing Synthesized Hydrocarbons and flown commercially as a suitable aviation fuel and also meets the United Kingdom's Ministry of Defense Standard 91-91 for Turbine Fuel, Kerosene Type, Jet A-1.

10. Types, prospective availability, and processing location of feedstocks contemplated for use.

The feedstock for Solena's plants can come from any carbon-based material. Solena's use of diverse feedstock comprising municipal solid waste, and agricultural and industrial waste, provides distinct advantages in terms of cost and efficiency to municipalities, rural jurisdictions, military installations, industries and utilities.

Please refer to section 2 above for a list of the feedstock that can be used in Solena's BTL facility. It should be noted however that although any carbonaceous feedstock can be used, Solena contemplates utilizing RDF, derived from municipal solid waste in its BTL project.

11. Capability and experience in the sale and delivery of aviation and marine diesel fuels.

At the present time, the first commercial size plant using biomass feedstock to be built and operate anywhere in the world will be constructed by Solena in London for British Airways. It is anticipated to be commissioned in 2014. Using this facility as an example, under Solena's guaranteed off-take contract for fuel delivery to British Airways, Solena's London facility will produce the bio-jet fuel and deliver it to British Airways tanker trucks at "the gate". The tanker trucks accept the bio-jet fuel and deliver it to the local airport where a blending capability exists. The bio-jet fuel is then blended with JetA or JP8 on a 50-50 basis, which meets the ASTM D7566 standard.

In the case of marine sustainable FTDiesel fuel, the first plant using the same model and as the bio-jet fuel plant will be built in Elizabeth, NJ. The off-taker is a large shipping conglomerate, which has partnered with Solena for the development of FT Diesel facilities worldwide. Under this partnership, Solena is required to pump the non-sulfur FTDiesel fuel into a tanker ship that will deliver and unload the FT Diesel to the freight ships at the terminal dock. This facility is expected to be commissioned in the second quarter of 2015.

12. Distribution methods available from the production facility

As described above, in the case of the biojet fuel, it will be stored and pumped into waiting British Airways tanker trucks, which then take the fuel to the airport blending facility.

In the case of marine sustainable FTDiesel fuel, it will be pumped to a waiting tanker boat docked in the water near the facility, which will then transport the fuel to a waiting freighter ship docked at the Port Newark-Elizabeth Marine Terminal.

13. Understanding of Federal, state, and local environmental laws and regulation, including Section 526 of the Energy Independence and Security Act (EISA) of 2007, and familiarity and experience with environmental compliance procedures and regulations for applicable states and U.S Environmental Protection Agency Regions.

Federal, State and Local Laws and Regulations and Incentives

With regard to our understanding of federal, state and local environmental laws and regulations, Arcadis has over a century of experience in the U.S. with planning and permitting in the energy sector. Arcadis has worked on facilities ranging from traditional fossil fuel-fired generating operations to renewable energy installations involving biofuels, waste-to-energy, hydropower, wind and solar. Arcadis' services have encompassed compliance with all environmental laws and regulations including those governing air, water, wastewater, solid waste, cultural, ecological, and threatened and endangered species. Based on this knowledge and experience, Solena and its partners do not foresee any challenges with environmental permitting or compliance for a biofuels facility employing Solena's technology in the U.S.

Solena and Arcadis have taken into account pertinent Federal, state and local laws and regulations, and local community relations, as it has developed its strategy for commercial scale production in the United States. Generally, Solena will leverage Arcadis' know-how and expertise to advise and assist the company in respect to compliance with environmental laws and regulations and to secure the necessary environmental and other permits in a timely and efficient manner.

The company will secure the necessary environmental approvals such as NEPA, permitting and other regulatory approvals in parallel with project development to the extent possible to ensure maximum speed to market and that individual projects are built on time.

Section 526 of the Energy Independence and Security Act (EISA) of 2007.

> EISA Section 526 states that "no Federal agency shall enter into a contract for procurement of an alternative or synthetic fuel, including a fuel produced from nonconventional petroleum sources, for any mobility-related use, other than for research or testing, unless the contract specifies that ***the*** lifecycle greenhouse gas emissions associated with the production and combustion of the fuel supplied under the contract must, on an ongoing basis, be less than or equal to such emissions from the equivalent conventional fuel produced from conventional petroleum sources."

Solena strongly supports Section 526 of the Energy Independence and Security Act (EISA) of 2007. Maintaining Section 526 will send an important signal to the advanced biofuels industry that the Federal Government, and most importantly the US military, intends to decrease its dependence on foreign-supplied fossil fuels and increase its diversification of fuel supply to include more renewable sources.

Arcadis has developed an excellent understanding of the implications of this element of the Act on fuel production from its work for the Defense Logistics Agency (DLA) – Energy on Carbon Capture, Sequestration and Reuse Opportunities for the Department of Defense. As part of this project, the Arcadis project team is currently working with the National Energy Technology Laboratory (NETL) on performing Life Cycle Analyses to confirm earlier NETL work that showed liquid fuels from coal/biomass mixtures were capable of achieving EISA 526 requirements if implemented in conjunction with carbon sequestration. The demonstration testing portion of this project will include gasification testing on coal/biomass mixtures designed to confirm the results of LCA modeling performed to date as well as provide the database for

future LCA modeling efforts. A biofuels production facility using Solena's technology will be compliant with the provisions of EISA Section 526.

14. Timing, duration, and volume of Government purchase contracts that would be required for fuel produced in a prospective commercial-scale facility.

The purchase contract for the prospective commercial-scale facility biofuel plants would begin once the plant begins operation 18-24 months after the commencement of construction

Solena's plants have an operating life of 20 years. To ensure finacibility, the facility would require a long-term fuel purchase contract of at least 10 years.

The plants that are currently under development produce 16 million gallons of bio-jet fuel or FT diesel over the period of one year. Solena envisions the Government purchase contract would be for the full 16 million gallons. However, the Government could purchase a smaller amount, as commercial demand is anticipated as well. Solena's strategy is to build its biofuel plants near airports, seaports, military bases so the transportation of the biofuel will be cost effective.

15. The types of documentation sufficient to assure the Government that an applicant would have adequate resources and sustained access to capital to successfully execute such a program

Prior to commencing construction of a proposed biorefinery, Solena and its financial partners would conduct a financial close, whereby all necessary funding and/or funding commitments and project supports would be committed to the project. The Government customer would be a party to the financial close and would be privy to all relevant closing documentation. Solena assumes that a Government customer would, in its fuel purchase agreements and any other agreements related to Government project supports, require documentation ensuring creditworthiness of the project and its participants. Factors to be addressed include:

- Economic viability and credit rating
- Cash flow sufficiency to service any debt obligations
- Scope and timing of equity commitments
- Demonstration of long-term supply feedstock and production off-take arrangements, including power purchase agreements where applicable
- Risk mitigation instruments for development, construction and operation
- Royalty payments

16. Types of assurances required to permit review by objective, independent consultants

Solena would require a customary non-disclosure agreement in order for objective, independent consultants to receive, review and handle any Solena proprietary and confidential information. Solena assumes that the typical review criteria used by Independent Consultants would involve:

- Pro Forma Financial Statement
- Fuel Procurement (Off-take) Agreement
- Feedstock Supply Agreement
- Power Purchase Agreement, if applicable
- Design and Technology Evaluation
- Fuel Quality Specification Report
- Pilot Reference Plant Performance Data
- Environmental Emissions Criteria
- Life Cycle Analysis (LCA) Data
- O&M / Warranty Data
- Facility Operational Plan

17. Top-level business plan/concept synopsis that provides insight into the mix of products to be produced, including any plans for non-fuel products or co-products, the biofuel customers to be targeted, and the importance and duration of any Government off-take agreements required to support successful implementation of the business model.

As the advanced biofuels industry in the United States is set to move beyond first generation, corn-based ethanol, Solena's plasma gasification and vitrification biomass to liquid (BTL) plants are moving toward commercialization. The partnership of the Federal Government with the private sector to speed the development of next generation biofuels is needed to spur near term demand in the United States of both commercial and government customers. The biofuels that may be generated by the plants include bio-jet fuel, FT diesel and bio-naphtha. The process also produces 33 MW (net to export) of electricity and an inert slag material that can be used for construction purposes. Solena's biofuel products are cost competitive with petroleum-based and other renewable fuels.

Burgeoning short-term demand for Solena's FT bio-jet fuel is being driven in the commercial sector by volatile oil prices, the European Union's (EU) emissions trading scheme (EU ETS, which from January of 2012 will require all carriers flying in and out of Europe to carry EU Allowances (EUA) to cover carbon emissions arising from their flights and operations) and increasing demand for, but limited supply of petroleum-based fuels. Both the Airlines and the EU estimate that airlines will spend up to €1.1bn when they join the EU ETS next year and rising to €10.4bn through to 2020.

In this context, the construction on Solena's British Airways plant that begins in the first quarter of 2012 could not come soon enough for BA. The London BA plant will be Europe's first bio-jet fuel plant. Solena also has letters of intent with Alitalia and Lufthansa for bio-jet fuel plants. American carriers, also subject to the EU ETS, have also shown great interest in Solena's FT bio-jet fuel. At the Paris Air Show in March 2011 Solena and the American Air Transport Association along with seven US carriers—American Airlines, United Holdings, Alaska Airlines, FedEx, JetBlue Airways, Southwest Airlines and US Airways—announced that the airlines had signed Letters of Intent (LOI) to purchase Solena FT bio-jet fuel. The aforementioned Gilroy, CA BTL plant will supply the above US carriers with 16 mmgpy of bio-jet fuel.

The Solena Q United States Public Sector strategy is focused on serving the Federal Government, municipal, rural, and commercial markets. Solena understands that there are increased efficiencies and market diversification in producing advanced biofuels for both the government and commercial sectors, and in particular, the United States military. In the near term, the US Air Force, which has certified FT bio-jet fuel for use in its aircraft and seeks to supply half of its domestic fuel needs from alternative sources by 2016, is the most logical customer, followed by the US Navy, Coast Guard and Army.

Global shipping companies already see the value and negotiations are underway to supply them with FT diesel. The FT diesel is attractive to trucking companies as well. As regulations become more stringent and public pressure for cleaner practices escalates, the demand for bio-jet fuel will continue to grow. In addition to the bio-jet fuel and FT diesel, the plants produce bio-naphtha, 33 MW (net to export) electricity and vitrified slag that can be used for construction material. The plans and uses for these products are outlined in the section entitled "Value-Added Co-Products" above.

The Solena BTL plants use patented, next generation, clean technology to convert biomass waste into useful products, i.e., renewable power and green biofuels that protect the environment. The plants produce no toxic ash, minimal air, water, and ground pollution, and minimal emissions that contain little or no SOX, NOX or particulate matter. GHG emissions are low and the CO2 produced is carbon neutral.

Additionally, communities will derive significant benefits from the construction of BTL plants. About 1,200 local green jobs will be created per plant. Communities will also be able to eliminate the cost of landfill waste and its negative environmental consequences, beneficially re-use that land, and not have to further allocate valuable land for landfilling.

Were Solena engaged in a project where the Government off-takes the primary biofuel, it would be important for the government to enter into an agreement that spans at least half the operating life of the plant, which is 20 years. If the contract for the off-take was shorter, there is a risk that another viable purchaser is not available, which would make it difficult to finance a project.

18. **Comments on the nature and level of Federal and State policies, incentives, and/or obligations (e.g. R&D, capital investment, investment or production incentives) needed to develop and sustain long-term domestic commitments to produce biomass-derived fuels. These may include use of existing programs, such as those administered by the U.S. Department of Agriculture (e.g. Commodity Credit Corporation and Loan Guarantee Program), the U.S. Department of Energy (e.g. Loan Guarantee Program), the U.S. Environmental Protection Agency (e.g. Renewable Fuel Standard, RFS2), and any other incentives, programs, or policies not currently available that would be necessary for successful project development.**

Solena's suggestions/recommendations are as follows:

- Provide long-term contracts (minimum 10 years) to purchase fuel. This is typically the minimum required commitment to obtain private sector financing. Provide capital

solutions such as debt financing and loan guarantees to accelerate incentive for the industry and to demonstrate Federal Commitment to the drop-in biofuels program.

- Continue/expand current DoD/DOE R&D efforts and loan guarantee programs.
- Provide some government owned storage/blending capacity for biofuel producers so they can concentrate on the production area rather than in the fuel blending/supply chain.
- Provide default criteria/standards for compliance with EISA 526 – i.e., by regulation or policy, declare that certain classes of fuels produced from specified sources using specified production methodologies meet 526 and do not require any type of supporting documentation so long as certification by the producer is provided.
- Provide flexibility so that other fuels can demonstrate compliance with EISA 526 by using a simple, straightforward, and well-defined LCA methodology.

Solena understands that the USEPA is in the process of developing guidance for the MSW Separation Plan that must be submitted to USEPA so that fuels derived from MSW feedstock can qualify as renewable fuels. The recycling/separation requirements as well as the submittal and approval process should be simple, consistent with current solid waste industry practices, take into account regional differences and be designed to encourage rather than discourage development of fuels from the entire MSW waste stream.

The Need for Policy Support and Long-Term Commitment to long-term incentives for the production of advanced biomass-derived fuels at the Federal, State and Local Level:

As this is a request from OSTP, Solena wishes to underscore the importance of long-term Federal Government policy support for renewable energy development and a clear signal to the markets of Federal, state and local commitment to long-term incentives for the production of advanced biomass-derived fuels. Policy s**t**ability and certainty are essential to developing an advanced biofuels industry in the United States. In particular, Solena supports the Federal and State policies and incentives currently in effect at the federal, state and local levels in the United States, and will pursue specific incentives as appropriate.

Federal Policies and Incentives

Federal Government General

- Provide some government owned storage/blending capacity for biofuel producers so they can concentrate on the production area rather than in the fuel blending/supply chain.
- Provide default criteria/standards for compliance with EISA 526 – i.e., by regulation or policy, declare that certain classes of fuels produced from specified sources using specified production methodologies meet 526 and do not require any type of supporting documentation so long as certification by the producer is provided.

Department of Defense (DoD):

National Defense Authorization Act of 2007 (NDAA): Along with EISA Section 526 and RFS2, the NDAA's provision on DoD sourcing 25% of all energy consumed from renewable sources is proving to be a key underpinning of the development of a viable advanced biofuels industry in the United States and should remain intact.

DoD Biofuels Contracting Authority:

- Provide some short-term willingness (3 – 5 years) to purchase biofuels at a premium above market value to accelerate incentive for the industry and to demonstrate Federal commitment to the drop-in biofuels program.

Quantity Requirements: The military and commercial customers may consider combining their respective advanced biofuel requirements and contracting efforts and communicate those combined requirements to industry.

Department of Energy (DOE): Biorefinery Project Grants, DOE Loan Guarantee Program, Loan Guarantees for Ethanol, and Commercial By-Products from Various Feedstocks

Environmental Protection Agency (EPA):

RFS 2: The Renewable Fuel Standard 2 (RFS2), which mandates the use in the United States of 36 billion gallons of renewable fuel by 2022, is of fundamental importance and serves as a cornerstone for the development of next generation advanced biofuels industry in the United States. Only 15 billion of that mandated number will likely come from corn ethanol. Companies such as Solena are positioning themselves for commercial-scale production and will supply millions of gallons—potentially hundreds of millions of gallons—mandated in RFS2.

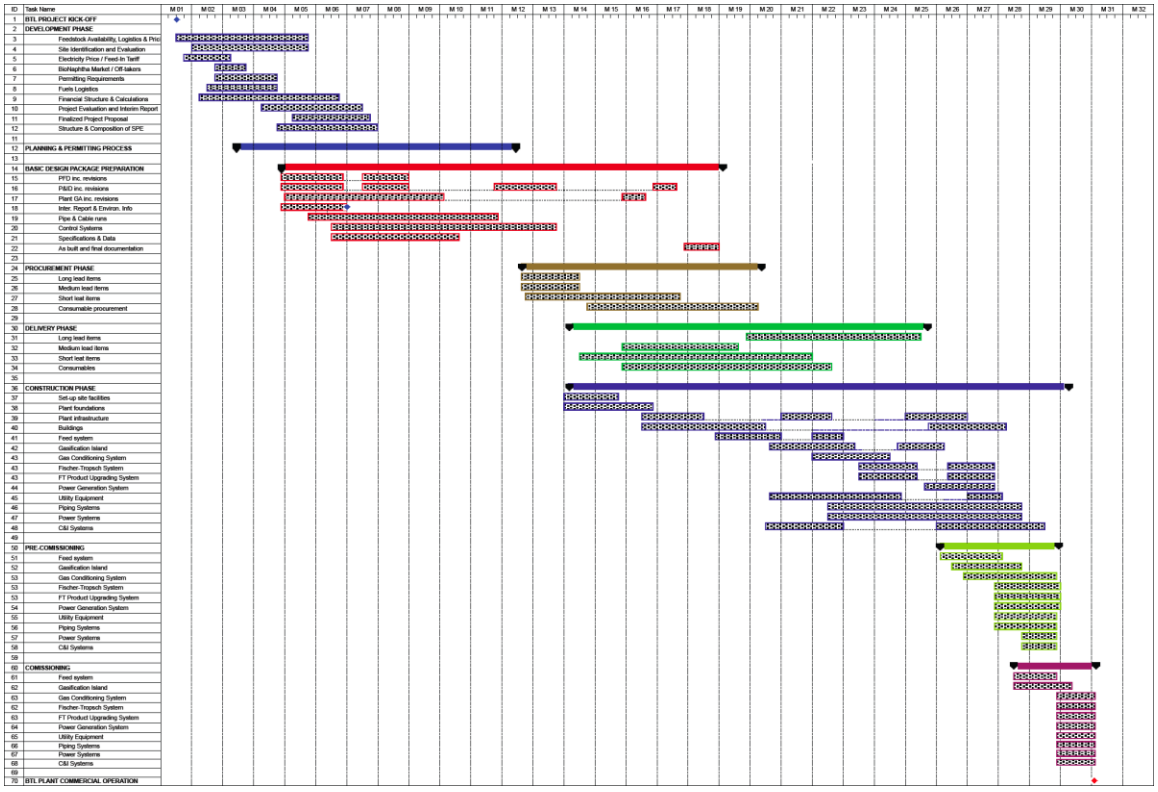
Department of Agriculture (USDA):

Solena believes USDA policy leadership and programmatic support is necessary to ensure the successful development of a commercial scale advanced biofuels industry and, in particular, a network of integrated biorefineries, in the United States. Many of the incentives listed below are set to expire in 2012. Industry will benefit from knowing that these programs and incentives will continue beyond 2012. Among the several USDA incentives programs, Solena may pursue the following programs:

Biorefinery Assistance Program□□Provides grants and loan guarantees for the construction and retrofitting of biorefineries that use renewable biomass to reduce or eliminate fossil fuel use.

Rural Energy for America Program (REAP): Provides grants and loans for a wide range of rural energy projects, including efficiency improvements and renewable energy projects. REAP is not specifically targeted at biofuels projects but could be a significant source of loan funds for such projects.

Estimated Project Timeline



1300 Pennsylvania Ave., NW ▪ SuiteG-0003 ▪ Washington DC 20004
Tel: 202-682-2405 Fax: 202-682-1843

Sent: Wed 10/19/2011 10:20 AM
Subject: bioeconomy idea

I'm the Pres and CEO of the Society of Physician Entrepreneurs at www.sopenet.org and linkedin group . We now have over 1500 international members and chapters across the US and around the world.

You should support our organziation to help create virtual biomedical and heatlhcare innovation networks throughout the US.

Arlen Meyers, MD, MBA
Professor, Departments of Otolaryngology, Dentistry and Engineering
University of Colorado
President and CEO, Society of Physician Entrepreneurs www.sopenet.org

Wed 10/19/2011 4:33 PM
Re: National Bioeconomy Blueprint

Dear Tom,

Please find attached my 2-page precis for the OST Bioeconomy RFI. If deemed worthwhile, I can provide an expanded version for the RFI.

Regards,

Franco Vitaliano
President & CEO
ExQor Technologies, Inc.

National Bioeconomy Pipeline

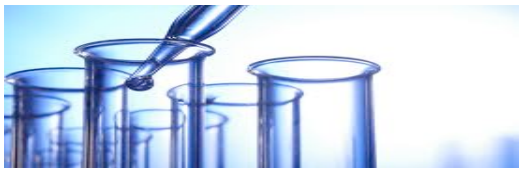
1. Secure, Web-based Pipeline Integration of Multipoint, National Rx & Research Data

Integrates US Agency, Corporate, University, Non-profit Data

2. National Bioeconomy Pipeline Spurs US Innovation

For US Agencies, Corporate, Universities, Non-profits, etc.

Simplified and rapid access of relevant, Pipeline-unified Rx and research data spurs new medical discoveries.



3. National Bioeconomy Pipeline Improves US Healthcare

3a. US Health Care Facilities

Facilities securely integrate, correlate & validate their data with relevant Pipeline data, spurs cost effective, improved, streamlined delivery of US medical services.

Patient History
Family history
Environmental data
Cost data
Insurance data
Other data

Imaging data
Lab data
Assay data
Genetic data
Phentotypic data
Epigenetic data
Other data

3b. Real Time Point of Care

Interactive, secure Pipeline access points rapidly return relevant results for up to date, real time point of care. Patient outcomes updated, correlated with National Pipeline, continually improves US medical results.

3c. HealthCare.gov

Easy to use, interactive, .gov access point utilizes relevant, non-confidential Pipeline data, provides US consumers up to date, pertinent medical, health care and insurance provider information.

Interactive Pipeline

POC Franco Vitaliano [redacted]

A National Bioeconomy Pipeline

A National Bioeconomy Pipeline can be used for creating new and innovative applications, from helping to accelerate and spur fundamental biomedical research, to helping calculate current national healthcare costs and formulating appropriate reimbursement strategies.

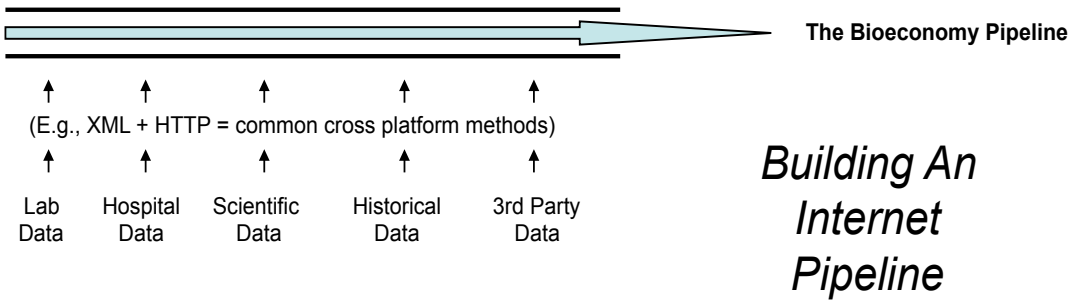
A National Bioeconomy Pipeline would be a powerful new computational approach for managing the exchange of information among various medical, healthcare and provider databases, devices, applications, etc.

The Pipeline would also maximize flexibility for addressing unexpected or new data types and healthcare events. It would also have the capability for interjecting human and creative insight into the global, real time Internet data flow.

A Pipeline is an Internet paradigm that handles vast quantities of heterogeneous data in real time, which allows seamless integration, fusion, and leverage of a multitude of point applications and captures multi-data types and events for discovery, analysis, design, deployment.

A National Bioeconomy Internet Pipeline can be defined as a data pipelining technique because it allows the exchange of information between data types without requiring them to be translated into the same format.

An Internet pipeline uses Web-based standards like XML, HTTP, HTTPS and others to build secure Web pipelines. The pipeline uses such standard techniques to non-disruptively overlay and make accessible otherwise landlocked data.



Data classification and analysis can be continuously improved by using previous results or by introducing additional related information into the pipeline.

Further, additional applications and tools can utilize and leverage the pipeline, like Google and Bing search engines, IBM's Watson natural language query system, or ExQor's cognitive systems for interjecting machine-level "self-knowledge" into the Pipeline.

POC Franco Vitaliano [redacted]

Sent: Wed 10/19/2011 11:25 AM
Subject: bio manufacturing

As a biotechnology entrepreneur trying to grow business provide a service and employee biotechnologist, it would be nice if the government would not use my taxes to fund my competition so they can undercut by prices. I don't understand how it can be justified that tax exempt academic institutions supported by my taxes can offer commercial for profit biologics manufacturing services to my potential customers. It wrong on many levels.
First it directs funding that should be directed to basic research to support essentially a commercial resource that already exists in the private sector and may thrive without government interference in the market. Research funding to support legitimate basic investigation into chronic diseases is scare enough without unnecessarily siphoning funds for these redundant and inefficient pet projects. Diverting funds to these facilities shows scientists at their worst. Academic institutions are poorly suited and staffed for the types of expertise and skill sets necessary for successful biologics manufacture. The facilities end up as backwaters for scientific failures.
Secondly it is anticompetitive and antibusiness to support these expensive facilities when they exist and can provide services to academic and commercial customers at significant savings to the taxpayer while providing significantly higher level of quality.
Thirdly there is a fairness issue where these facilities are being exorbitantly funded with taxes generated in part by their competitors. Like all life sciences entrepreneurs I strongly support funding for NIH, NSF, basic research, directed disease research as the fuel for our bioeconomy. I have worked at NIH and served as a PHS officer. But to have academic facilities that compete in the commercial arena is intellectually unsound, wasteful of limited healthcare R&D funding, and unfair to life sciences entrepreneurs.

Best Regards,

Dale VanderPutten MBA, PhD
Chief Executive Officer
Omnia Biologics, Inc.
(301) 984-5928
www.omniabiologics.com

Sent: Thu 10/20/2011 1:43 PM
Subject: Response to RFI re National Bioeconomy Blueprint

To the Office of Science and Technology Policy:

I am a former biomedical scientist, serial biotechnology entrepreneur, and management professor, and a current angel investor and adviser to operating companies and investment firms. I also co-founded and was the first president of the Industrial Biotechnology Association, which today is known as the Biotechnology Industry Organization.

I am responding to the Request for Information "regarding recommendations for harnessing biological research innovations to meet national challenges in health, food, energy, and the environment while creating high-wage, high-skill jobs." In particular, I would like to address the 8th question listed in the RFI, "What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?"

In general, the real engine behind job growth is the entrepreneur because small businesses account for half of all private sector jobs, and those growing most rapidly require equity financing from angel investors and venture capital firms. Equity financing is especially important for the biotech industry, because most biotechnology products are heavily regulated and take one or more decades to enter the marketplace. Therefore, over time biotech companies require a number of rounds of investment capital, amounting to hundreds of millions of dollars and even exceeding a billion dollars.

I have previously published several articles that describe how the federal government could really stimulate job growth and reduce the deficit at the same time. The key to the underlying strategy is for government to provide the right kind of environment for the private sector to turn the economy around. For reasons explained in the preceding paragraph, providing such an environment is particularly germane to the biotechnology sector and as a result would foster the development of breakthrough products in areas as diverse as personalized medicine, nanobiotechnology, biofuels, and agricultural and industrial biotechnology.

Three new government policies, if enacted together, would increase the availability of equity financing and stimulate the economy, leading to reduced unemployment and a decrease in the deficit.

Prior to the recent recession, American angel investors and venture capital firms together invested over $45 billion annually. One proposed policy would provide tax credits equaling 25% of all qualifying investments, in return for government receiving 25% of applicable capital gains. The availability of capital might then increase by 33% or $15 billion, from $45 billion to $60 billion, since the net cost to investors of $60 billion invested would remain at $45 billion.

Compared to the current system, which is subject to a 15% capital gains tax, both the government and the investor would enjoy a higher net return. The net return on the same net investment would increase by almost 18% for the investor and over 122% for the government. Most importantly, historical data indicate that additional venture investments of $15 billion per year would create an additional 1.3 million jobs over a 5-year period.

Moreover, if over the next 20 years angel investors and venture capital firms earned between 50 to 100% of what VC firms averaged for the 20-year period ending December 31, 2007, the government's 25% share in an annual average of $60 billion invested would yield between $770 billion and $2.2 trillion.

Many more high-risk start-ups exploiting state-of-the-art technologies would be funded, resulting in a net total of 6.8 million jobs created.

The second proposed policy would be for the government to invest in VC firms. If over the next five years the U.S. government invested $15 billion annually in VC firms, another 1.3 million jobs would be created. Over a 20-year period, such an investment would result in another 6.8 million more jobs created, and the government would earn another $770 billion to $2.2 trillion from its investment.

The key to implementation of this proposal is to establish a formula by which federal funds are transferred directly to VC firms without the government trying to pick winners from losers. All investment decisions made by the participating VC firms would be left exclusively to the VC firms' general partners.

Each year the budgeted amount of federal funds targeted for VC firms would be disbursed in proportion to the magnitude of the private sector funds they manage. Thus, if in a given year, all those VC firms desiring to accept federal funds managed a total of $100 billion, a participating firm managing $1 billion, representing 1% of the $100 billion, would be eligible to receive $150 million, representing 1% of the government's $15 billion investment.

The third proposed policy would exempt public companies with less than one billion dollar revenues from complying with the onerous regulations of the Sarbanes-Oxley Act. Privately held companies shy away from going public because of the expense and time required to comply with Sarbanes-Oxley. As a result, privately held companies typically opt to be acquired, since that tends to be the only viable exit strategy for investors. Unfortunately, whereas initial public offerings lead to increases in employment, acquisitions are more likely to result in layoffs in order to reduce fixed expenses. Repealing Sarbanes-Oxley for young, relatively small but rapidly growing companies would cause a surge in both IPOs and new jobs.

In summary, by providing tax credits to angel investors and venture capitalists, investing in VC funds as a limited partner (according to a fixed formula), and repealing Sarbanes-Oxley for small public companies, the government could foster the creation of several million jobs and the commercialization of exciting new technologies, and in addition earn over a trillion dollar return. The impact on biotechnology research innovations would be enormous.

I have attached links to three relevant articles I have published in Genetic Engineering and Biotechnology News, which provide more detail regarding the above proposals. I am also willing to volunteer my time to help the Office of Science and Technology Policy develop a National Bioeconomy Blueprint.

J. Leslie Glick

Sent: Thu 10/20/2011 4:07 PM
Subject: Bio Economy - clear message on people owning their own data needed

Dear Sir/Madam,

You might want to take a look at this 2 minute demo on integrating personal genetic data with the web. http://www.screencast.com/t/ISu0thJq . It's based on an issued patent for managing personal genetic data on the web.

It shifts the power of genetic data from biotech/pharma and health entities (that haven't created wealth) to individuals.
It might be able to provide the foundation for a new form of wealth creation.

A genome is a data file format representing a digital human being - we need to get this right.

Sincerely,

Alice Rathjen

ExQori△

A Cognitive Pipeline Platform For the Internet

ExQor Technologies, Inc.

Boston MA USA
Tel 617 742 4422

Background

The Internet

Global system of interconnected computer networks that use the standard Internet Protocol Suite (TCP/IP) to serve billions of users worldwide.

The World Wide Web

A system of interlinked hypertext documents accessed via the Internet, typically by using a web browser.

Search Engines

Software platforms for searching for information on the Internet and the Web. Passive systems, require user to formulate and refine search queries, put results into meaningful context.

Social Media

Software platforms for the Internet, Web, and mobile telecommunications. Enable a global social structure made up of individuals or organizations, connected together by one or more types of interdependency, such as friendship, kinship, common interest, financial exchange, dislike, sexual relationships, or relationships of beliefs, knowledge or prestige. Passive systems, rely on their users to supply content, individual and collective context, linkages.

Internet Pipelines

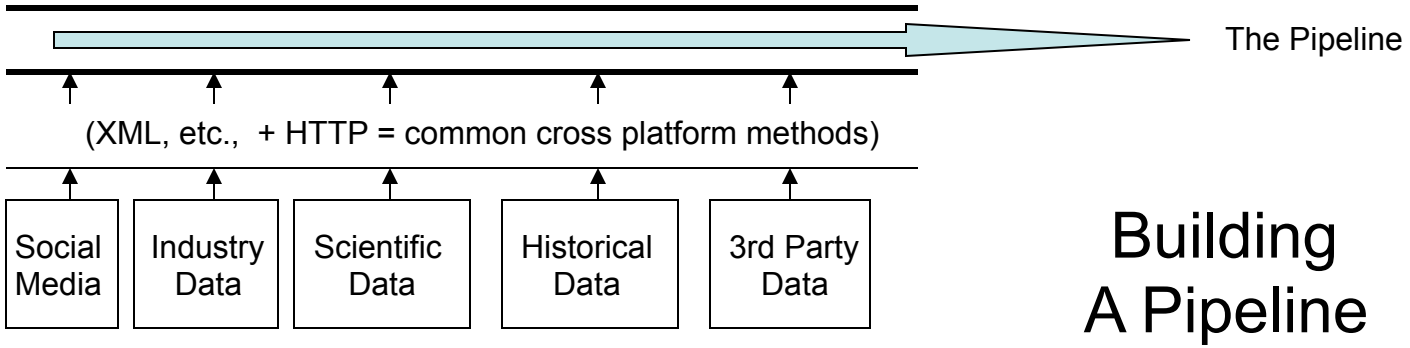
- A new type of software platform for the Internet, Web, mobile telecommunications, social media, & more.
- Uses Internet and Web standards to globally integrate data, systems, social media, and devices.
- Non-disruptive overlay to existing data.
- Allows exchange of information between data types without requiring them to be translated into same format.
- High throughput.
- Can be highly proactive or passive.
- Can be very intelligent, proactively assist users.
- Highly interactive correlation of real time events, data, social interactions.
- Can put all available elements into global or highly individualized context.
- Can enable highly personalized services.

Current Issues

- Data integration requirements in today's large scale, multi-departmental, globally distributed environments present highly complex data management challenges.
- A wealth of data, including historical data, lab data, sensor data, analytical data, field data, third party data, social media, and other data are continuously being generated, collected, and in some cases, simulated.
- High-throughput technologies have created an information processing crisis by generating vast amounts of disparate data that must be processed and analyzed.
- Only with intelligent, highly automated information processing technologies and tools will naïve users, researchers, and expert users be able to identify and qualify high value data targets, and develop products and business strategies to respond to these lucrative targets, at the accelerated pace now required.
- *Internet Pipelines are the solution to the problem.*

Internet Pipeline

- An Internet pipeline is a new information processing paradigm that can handle vast quantities of heterogeneous data in real time, that allows seamless integration of the multitude of point applications that have sprung up and captures multi-workflows for analysis, design, deployment, and compliance reasons.
- Internet pipelining is a computational approach to managing the exchange of information among various data in order to maximize both the flexibility for addressing unexpected data types and the potential for introducing creative insight.



Building A Pipeline

ExQori$\underline{\Delta}$,
A Cognitive Internet Pipeline

A new kind of Internet pipeline:

- It is a Cognitive Pipeline system.
- It intelligently does the work for you.
- Puts its results into highly individualized user context
- Automatically stays abreast, intelligently examines continually changing data and user requirements.

ExQoriΔ

ExQoriΔ Cognitive Pipeline

Automatically answers the hard questions:

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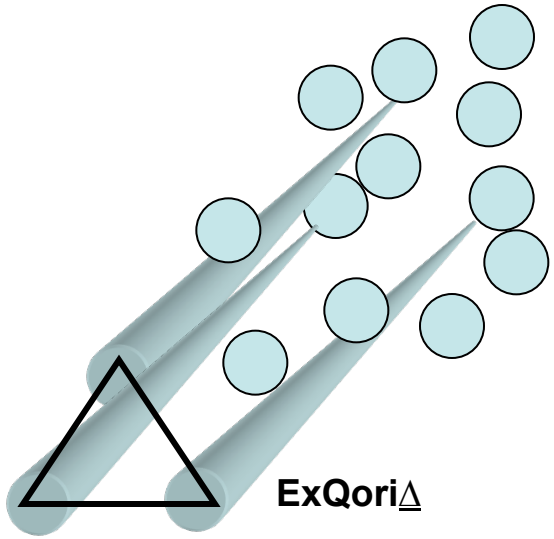

Finding & discerning results, meaning, putting them into proper context, staying abreast in real time.

ExQoriΔ

Key Characteristics

- ExQoriΔ Cognitive Pipelines:
  - Employ and integrate multiple types of discovery strategies;
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  - Deliver highly individualized, pertinent, real time results based on their growing self-knowledge, perception, reasoning and cognitive faculties.

***ExQori*Δ** Cognitively Transforms The Pipeline

ExQoriΔ Cognitive Pipeline

- **Self-knowledge —** Can identify its purpose and understand its internal functions.
- **Perception —** Has the ability to self-recognize, interpret, and understand highly complex inputs.
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- ExQoriΔ automatically formulates complex queries and actions.
- Intelligently real time iterates across heterogeneous data elements and sources.
- ExQoriΔ's cognitive algorithm is a data pipelining technique because it allows the exchange of information between data types without requiring them to be translated into the same format.

ExQori$\underline{\Delta}$

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Boston MA 02114-2818 USA

Tel 617 742 4422

Contact: Franco Vitaliano
e-mail: francov@exqor.com

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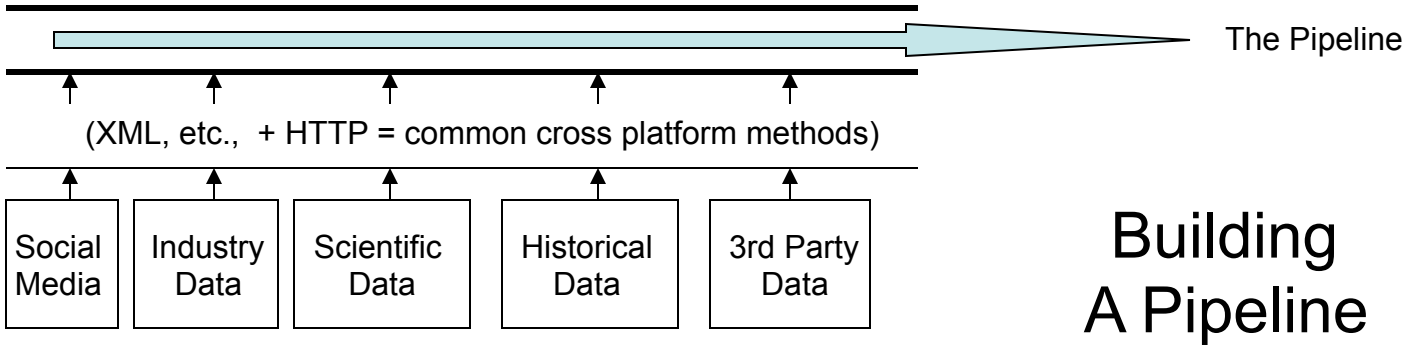

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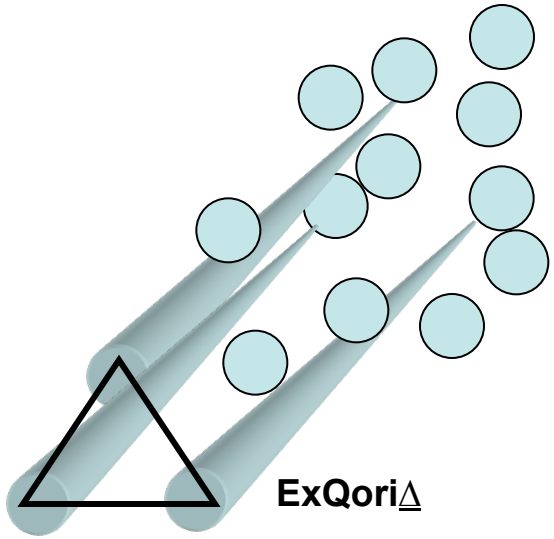

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Contact: Franco Vitaliano
e-mail: francov@exqor.com

Fri 10/21/2011 11:32 AM
Long-term bio-economy consideration

As part of our projections into the future, I'd like to see us remember the very long-term future in terms of the effects of the bio-economy. A biofuels supporter, I'm also concerned about the long-term health of U.S. soils, and would like to know that there is more research (and attention paid) on how MUCH biomass of any kind can be removed from the soil without corresponding replenishment. I'd like to see research and, ultimately, (bio)economic policies, that acknowledge that we must re-build the soils upon which society rests; and that this focus - admittedly a very longterm view - differs significantly from current general practices of value extraction.

I'd like to see research support on how we may most effectively capture that which is currently labeled "waste" (most obviously, sewage, and, e.g., the phosphates lost to the soils by our current practices of waste handling) and address the need to return value to the soils that underlie life, including the bio-economy. Perhaps this is a long way of saying that I'd like to see continued - perhaps expanded - support for research and policies designed to make our society's economy sustainable over generations.

Thank you for providing this opportunity to comment!

Regards,

Robert T. Nuner

Fri 10/21/2011 11:48 AM
Subject: Suggestion

Make oil from algae.

Ron Grow

Sent: Fri 10/21/2011 12:10 PM
Subject: Advice on Bio - fuels

Good day,

I looked at your questionaire and felt it warranted a reply.

Firstly the main consideration is to free ourselves from the constraints of OPEC over our Military and our economy utilising their imported crude oil with all the cost and political ramifications.

Secondly our country has done amazingly well in a short space of time making Bio - fuels that work.
I refer to

a) Bio - Diesel from its various sources.

b) Bio Jet - fuel The military and civilian aero industry have done a lot of successful testing in fact they could switch over within 2 years , just converting existing plants to manufacture Bio - jet would save billions of dollars.

c) Bio fuel Ethanol, Gasoline alternative, here the government is partially on the wrong track, sure Ethanol works but is difficult to transport, to store and to use ,harmful to gasoline engines over time . also lower energy outputs and a short shelf life.

What should be considered very quickly ...is converting existing Ethanol plants to BIO- BUTANOL , this product is much more stable ,easier to transport, less prone to evaporation, has similar energy outputs to gasoline, stores well.

Dow and BP have already converted some of their plants to Bio Butanol which has more uses as well from the end and from by- products. similar costs as gasoline to manufacture, safer to workers , public and servicing personnel.

With regard to the BIO MASS required to manufacture the above fuels enough has been said and tested i will however add that Algae is the non ending source of the future, now that low cost methods have been found to extract the oil from the algae cell.More R&D in this area will be money well spent.

I do hope that someone reads this note and that it helps .
Thank you

Fri 10/21/2011 2:50 PM
RFI - Building A 21st Century Bioeconomy

Attached is a Master Thesis Report from Boras University in Sweden done on Pure Lignin Environmental Technology Ltd. biomass pre-treatment process as compared to other current processes, showing the superiority of PLET's process and that its cellulose yields much more ethanol than the others!

The Environmentally friendly process also produces a superior grade native-form lignin (soluble, high molecular weight) and hemi-cellulose.

For more information on our process and products please check our website at: www.purelignin.com

Thank you.

Best regards,

Lani O'Flynn
Pure Lignin Environmental Technology Ltd.
Kelowna B.C., Canada

HÖGSKOLAN I BORÅS
INSTITUTIONEN INGENJÖRSHÖGSKOLAN

Teknisk och ekonomisk utvärdering av en ny miljövänlig förbehandlingsmetod av biomassaavfall med utspädd salpetersyra

Technical and economical evaluation of a new environmentally friendly pre-treatment method of biomass waste by dilute nitric acid pulping

Written by

Li Zhi

Oliver Murgårdh

A Master Thesis, which is a compulsary assignment in Master in Industrial Biotechnology, Master Programme – Resource Recovery, 30 ECTS credits
No. Exjobbsnummer/2011

Svensk titel: Teknisk och ekonomisk utvärdering av en ny miljövänlig förbehandlingsmetod av biomassaavfall med utspädd salpetersyra.

English Title: Technical and economical evaluation of a new environmentally friendly pre-treatment method of biomass waste by dilute nitric acid pulping.

Authors

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Master Thesis in Resource Recovery

Subject category: Biotechnology

Högskolan i Borås
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501 90 BORÅS
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Examiner: Mohammad Taherzadeh

Supervisor: Tomas Brandberg

Supervisor, address: Högskolan i Borås

501 90 Borås

Commissioner: Högskolan i Borås

Date of approval: 2011-10-xx

Key words: Lignin, Cellulosic ethanol, Sweet liquor.

Abstract

Bio-refining of renewable resources such as waste biomass into value added products has increased rapidly over the decades. The aim is to find new environmentally friendly yet economically feasible ways of replacing current utilization of non renewable resources. It can be expected that commercially viable next generation bio-ethanol will be produced from lignocellulosic feedstock in the near future.

This master thesis aims at providing a technical and economical evaluation of a recently patented pre-treatment method of biomass wastes which uses dilute nitric acid pulping. Evaluation of producing next generation ethanol from dilute nitric acid pre-treated cellulose rich softwood was performed and sulphite weak acid pre-treated hemi-cellulose rich hardwood Birch pulp was used as a comparison. Experiments were conducted on laboratory scale, using samples from two companies, referred to as Pure Lignin Environmental Technology Ltd (=PLET) (Canada) and SEKAB E-technology (Sweden). The strategy of PLET is currently to find a commercial platform to produce value added products from waste biomass generated by saw mills and pulping industries, while SEKAB E-Technology mainly works with Swedish softwood as a raw material.

The technical part of this Master thesis includes a series of fermentation trials using either SSF (=Simultaneous Saccharification and Fermentation) or SHF (=Separate Hydrolysis and Fermentation). The yields of the enzymatic hydrolysis and subsequent fermentations were estimated with HPLC measurements. The economical part of this master thesis includes the use of Business Model Canvas to define the basic topics and tasks that need to be addressed in the upstart phase of a small consulting bio-tech company.

Summary

Experimental data support the possibility to make lignocellulosic ethanol out of either softwood or hardwood. Ethanol yield from dry material obtained for hardwood birch slurry was 0,43 (g ethanol / g dry raw material). Ethanol yield from dry material obtained for softwood pine washed cellulose was 0,32 g (ethanol / g cellulose). Ethanol yield from dry material obtained for softwood pine unwashed cellulose in the three SHF was 0,48; 0,34 and 0,28 (g ethanol / g cellulose) respectively, while the yield in the two SSF was 0,37 and 0,38 (g ethanol / g cellulose).

The question is if technology provided by PLET can be applied on a commercial, industrial scale, hence the approach is to simulate an industrial full scale process as much as possible in a laboratory environment.

Bio-refining, is at present a rapidly expanding field and it is difficult to tell what will be the next commercially viable process. Therefore, information of what really is cutting edge in the field is essential. In this context, PLET stands out with an interesting new approach to pre-treat waste biomass into value added products, and has therefore received much attention in this master thesis.

Contents

1. Background

This master thesis set out to look at a specific Canadian company in depth (Pure Lignin Environmental Technology Ltd), known as PLET henceforth. PLET has a new approach with a recently patented environmentally friendly technology, which could be extremely lucrative if applied in the right context.

It is desirable to look at the possibility of using the master thesis as a take-off platform to launch a consulting bio-tech company directly after completion. The idea is to accumulate enough knowledge in bio-refining, a relatively new and promising field of science. That is, to study how value added products could be produced from waste biomass.

In addition, economical aspects of such a technical application must be addressed at an early stage of development. This cross-linkage of consideration and understanding between different academic disciplines is necessary to apply as early as possible, in order to save both time and resources. This master thesis aims to consider both the technical issues as well as economical issues.

Last but not least, extensive networking was needed in order to make valuable connections through emails, phone calls, business meetings, conference visits, study visits, scholarship applications, as well as information gathering via consultation by professors. The above mentioned activities have received much attention throughout the project, in addition to experimentation in laboratory. Networking of this kind is absolutely necessary in order to establish a foundation for a future company. However it is difficult to display in an academic report of how much effort that really has been put into this, since it is hard to explain in scientific terminology.

The original plan was to investigate whether the technology of PLET could be used as a commercial platform in Sweden, with laboratory results backing-up a business argumentation. Promotion of the technology could be performed with a mobile factory housed on trucks for demonstration purposes. In this way, a possibility was envisioned to take care of excess saw dust and wood chips along with bark residues and even other products such as black liquor from smaller up to medium sized saw mills and paper pulp industries, by using a somewhat larger version of the already existing mobile demonstration plant of PLET.

2. Introduction

2.1 Master thesis focus

The topic on which this master thesis focuses is next generation lignocellulosic ethanol production with SSF (=Simultaneous Saccharification and Fermentation) and/or SHF (=Separate Hydrolysis and Fermentation), with new enzymes Cellic Ctec2 and modified yeast such as Ethanol Red and a pentose fermenting strain. Raw material used in the experiments was pre-treated biomass samples (pine and birch) supplied by PLET and SEKAB E-Technology, respectively.

2.2 Biomass characterization: Cellulose / Hemi-cellulose / Lignin

2.2.1 Categorization of biomass

Biomass can be divided into five basic categories including virgin wood (= softwood and hardwood); energy crops such as rape seed, agricultural residues such as wheat straw, industrial wastes, such as discarded packaging material, old construction timber and finally food waste such as orange peels [1].

Softwoods are for example gymnosperms like spruce and pine, whereas hardwoods are woody angiosperms such as oak and birch. In addition to hardwood and softwood there are annual plants, also known as herbaceous angiosperms. Fractions of lignin, hemi-cellulose and cellulose vary a lot between different plant species. The general structure of the ligno-cellulosic matrix in common wood is presented below [2].

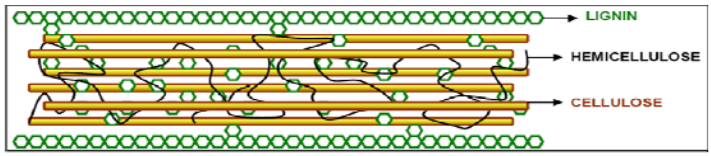

Figure 1. *The lignocellulosic structure in virgin wood displaying the fractions lignin, hemi-cellulose and cellulose.*

2.2.2 Description of cellulose

Cellulose is the main structural component in plants. It consists of unbranched chains of β-D-glucose units closely packed in parallel fiber structures. The CH_2OH- groups are alternating above and under the plane of elongation. Cellulose fibers are usually 2-20 nm in diameter and about 100-40000 nm long. Cellulose generally consists of 2000-14000 residues held flat by hydrogen bonds and is insoluble in water due to its network of hydrophobic ribbons that faces outwards. Structural unit of cellulose is called β-(1→4)-D-glucopyranose [3] [4].

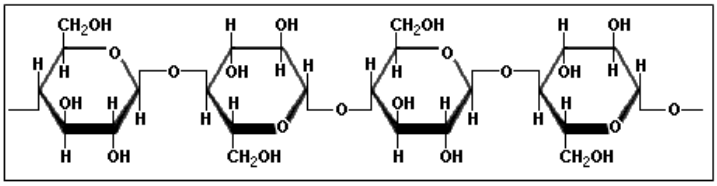

Figure 2. *Example of the chemical structure of cellulose β-(1→4)-D-glucopyranose.*

2.2.3 Description of hemi-cellulose

Hemi-cellulose is branched and built up mainly from D-xylose and other sugars. The content of hemi-cellulose is generally higher in hardwoods compared to softwoods, but it is in both cases a major structural component. Annual plants (=herbaceous angiosperms) have even greater percentage of hemi-cellulose embedded in its structure. One common component in hemi-cellulose is xylan, which contain multiple D-xylose units with β-(1→4)-linkages [4].

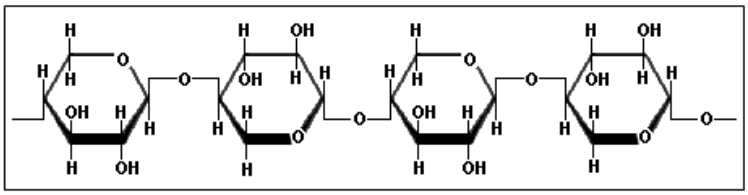

Figure 3. *Example of the chemical structure of hemi-cellulose (Xylan).*

2.2.4 Description of Lignin

Lignin is a main component in vascular plants, such as trees, bushes and grass. Lignin is one of the most abundant organic polymers on Earth, occupying ≈ 30 % of non-fossil organic carbon and constituting from a quarter to a third of the dry mass of wood. A fiber originates from the cambium as a living cell but soon loses its components. These fibers are then developed as a thickened secondary wall, which is made from cellulose, hemi-cellulose and lignin. Cellulose is strong in tension, while lignin is strong in compression. A figurative comparison could be made with reinforced concrete, where steel is the cellulose fibers and the concrete is lignin and hemi-cellulose [5].

The basic structure of lignin is built from three monolignol monomers. These are methoxylated to a varying degree. The three monomers are P-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol, incorporated in lignin polymers in the form of phenylpropanoids, also known as guaiacyl (=G), syringyl (=S) and *P*-hydroxyphenyl (=H). All lignins contain small amounts of incomplete or modified monolignols, and other monomers are prominent in non-woody plants [6].

There are three types of plants which are rich in lignocellulosic material; softwood (=gymnosperms), hardwood (=woody angiosperms) and annual plants (herbaceous angiosperms). Gymnosperms have a lignin that consists almost entirely of (G) with small quantities of (H). That of dicotyledonous angiosperms is more often a mixture of (G) and (S), with very little (H). Monocotyledonous lignin is a mixture of all three phenylpropanoids. Many grasses have mostly (G), while some palms have mainly (S) [6].

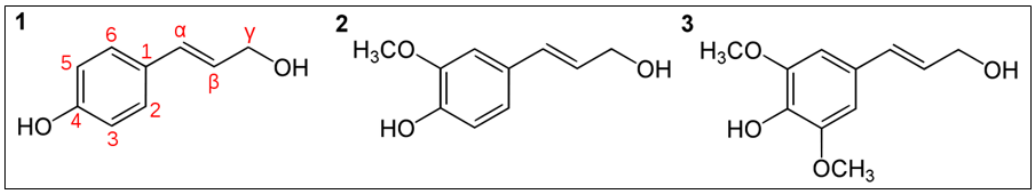

Figure 4. *Chemical structure of the three basic phenyl propanoid monomers which are the building blocks of lignin, also called monolignols.* ***1*** *= Coniferyl alcohol,* ***2*** *= Sinapyl alcohol and* ***3*** *= p-Coumaryl alcohol. Red numbers and greek letters in the figure define carbon positions.*

2.3 Bio-refinery emerging

Today there are great expectations for the benefits that can emerge from biotechnology. Especially, what could be done with the three major components cellulose, hemi-cellulose and lignin, found in abundance in lignocellulosic biomass? Expectations are particularly evident when looking at the world's stock market exchanges, where there are a lot of speculations of how fast future development will be. In some cases, these anticipations could be unrealistic, but are nevertheless inspiring, given the fact that mankind as a whole somehow has to solve the supply of energy in the future, mitigate the greenhouse effect and find a sustainable approach to co-exist with nature and at the same time maintain economic development.

Biotech solutions provide a platform to convert our society's use of non renewable resources, like the use of crude oil, to environmentally friendly utilization of renewable resources. In this context, conversion of waste biomass into cellulosic ethanol is an easily comprehensible and logical step. Currently, waste biomass is abundant and relatively cheap to purchase and has a huge potential as a raw material, suitable for processing into high grade commercial products, given that the constituents can be purified at a low cost and with minor environmental impact. Still there are many problems to be solved in bio-process design and optimization of bio-refining, since it is a relatively new and immature technology. This is, about to change.

2.3.1 Major pre-treatment options in Bio-refining and how they are funded

The general purpose of a pre-treatment of biomass is to expose the embedded cellulose and hemicelluloses from the lignin matrix, thus allowing enzymatic hydrolysis of sugars in the subsequent fermentation. There are several techniques in use to achieve this today [7]. The European Union has allocated resources to support research in strategically important areas. This is mainly done within the framework programs issued by the European commission. There are of course many other research projects within the EU, as well as there are independently funded projects with no governmental or political involvement.

A common approach is to use the SO_2-treatment or dilute acid treatment, which to a large extent hydrolyzes the hemicelluloses, while leaving a large part of the lignin still connected to the cellulose fibers. This technology is performed by SEKAB E-Technology among others. Another method is the steam explosion, which physically disrupts the biomass structure. Lignin remains attached to the fibers. Thirdly, there is the ammonia fiber explosion (AFEX), uses alkaline conditions to allow enzymes access to the cellulose and hemicelluloses. Fourthly, there is the expensive Organosolv approach, which hydrolyzes and removes the lignin and other components from the fibers.

Neither of these methods has yet paved the way for a commercial breakthrough. A method which is today practiced by SEKAB E-Technology and other companies is to pre-treat the cellulose material chemically in order to partially disrupt the structure and subsequently expose it to cellulase enzymes. The advantage with enzymes is that the conversion from cellulose to monomeric sugars is selective, which allows for higher yields. The disadvantage, again, is the cost and probably the enzymatic approach will require on-site production of cheap cellulase enzymes.

2.3.2 The sugar platform

The sugar platform could be defined as a generic value chain including the production of transport bio-fuels such as ethanol and butanol, plastics like PLA (=Poly Lactic Acid), food additives like amino acids and vitamins as well as medical applications like antibiotics and hormones. The refining within the sugar platform uses expertise in both chemistry and biotechnology.

In general terms the sugar platform stands for use of a renewable raw material usually processed from wastes from the paper and pulping industry, which is then refined to a product with higher value. One of the best and well known examples of this is the extraction of xylose from hexose rich pulp at sulphite pulp mills and its refining into xylitol and bio-ethanol.

Wood chips are preferably used as raw material for pulp production while saw dust is incinerated to make bioenergy for other processing or production of district heating. It is likely that the best sugar sources for bio-refining are found among the wet carbohydrate rich by-product waste streams in the conventional paper and pulping industry [8].

2.3.3 Projects in the past

NILE, New Improvements in Lignocellulosic Ethanol, stretched over a period of four years (2005-2009). NILE was supported by the European commission's 6th framework programme. Through this programme resources were allocated to support SEKAB E-technology's research. One of the many topics addressed, was the improvement of enzymatic hydrolysis, since this process step is estimated to contribute to about 30-50% of the cost of the ethanol production process when a lignocellulosic feedstock is used. Another topic addressed is the development of new types of yeast for fermentation of sugars into ethanol [9].

All lignocellulosic material must undergo pre-treatment, if the enzymes are ever going to reach the cellulose fibers and perform their task. The NILE project has addressed several approaches to find suitable pre-treatments. In general terms, a standard pre-treatment include conditioning (size reduction and impregnation) of the raw material followed by a thermo-chemical process to break up the lignocellulosic matrix.

Attention within the NILE project was focused on *Trichoderma reesei*, a fungi known for its cellulase production. *T. reesei* produces nine major enzymes which are utilized in enzymatic hydrolysis of lignocellulosic material. The enzymes *T. reesei* provide could be categorized in three distinct types of activity; two are cellobiohydrolases which liberates cellobiose, five are endoglucanases which attack the cellulose at random points and finally there are two β-glucosidases which splits cellobiose into glucose units.

If the enzymatic hydrolysis is successful, the result is a mixed sugar solution ready to be fermented by yeast into ethanol. Fermenting strains used must possess inherently good tolerance to both high levels of ethanol concentration as well as inhibitors. This has resulted in an improved xylose fermenting capacity as well as a reduced lag phase [9].

2.4 Enzymatic hydrolysis of lignocellulosic material

All enzymatic hydrolysis of lignocellulosic material requires pre-treatment. Enzymes are regarded as a good compliment to dilute acid hydrolysis. In bio-refining, concentrated acid hydrolysis should be contrasted with dilute acid hydrolysis. Dilute acid hydrolysis can be performed with or without enzymes. Without enzymes conditions must be harsh in order to get a good yield. Harsh conditions imply formation of inhibitors and additional losses of sugars due to formation of by-products. With enzymatic treatment the need for harsh pretreatment is reduced. In addition, enzymatic hydrolysis can be performed with lower energy consumption and much reduced environmental impact. Concentrated acid hydrolysis works well technically, but has problems with corrosion on equipment and expensive recycling of chemicals used in the process.

In enzymatic hydrolysis, the yield of pure glucose is high, as is the decreased formation of inhibitory by-products, which is favorable for a subsequent fermentation into ethanol. Cellulases in enzymatic hydrolysis of lignocellulosic material are aws follows; β-1-4-endoglucanases, β-1-4-exoglucanases or cellobiohydrolases and β-glucosidases. Enzymes such as β-1-4-endoglucanases attack regions of low crystallinity, thus creating free chain ends. Then there are β-1-4-exoglucanases or cellobiohydrolases, which removes cellobiose units from the free chain ends. Last but not least, there are the β-glucosidases, which hydrolyzes cellobiose into glucose units [2].

Cellulases (=enzymes which degrade cellulose), are needed to break down the cellulose fibers into fermentable sugars. This process is called enzymatic hydrolysis and the goal is to obtain as much D-glucose units possible from the pre-treated lignocellulosic material. One of the arguably most cost efficient enzymes available today is the Cellic Ctec 2, supplied by Novozymes. The current commercial variant, Cellic Ctec 2 has already reduced enzyme cost by 50%, to as low as 0,5 US dollar/gallon produced ethanol [10].

Active enzymes in Cellic Ctec 2 are based upon extractions of GH61-proteins and genes expressing them are inserted into the filamentous fungi *Trichoderma reesei*. These glycoside hydrolases (=GH) catalyze the hydrolysis of hemicelluloses and celluloses. The GH61-proteins lack to a large extent measureable hydrolytic activity by themselves, but in the presence of a divalent metal ion the protein loading is significantly reduced. The structure of one highly active GH61- protein has been solved and the results indicate that it is not a glycoside hydrolase. This is because it is devoid of conserved juxtaposed acidic side chains which would otherwise serve as the general proton donors and nucleophile/base in the hydrolytic reaction. Enhancement of cellulase activity by GH61 is not limited to just dilute acid pre-treated biomass but could also be used on steam-exploded biomass as well as on organosolv pulps. Surprisingly, the efficiency of the enzymatic activity does not work better on pure cellulosic substrates, rather is the opposite is favored. An unusual reaction mechanism for the hydrolytic catalysis cannot be ruled out [11].

2.5 Fermentation techniques

Fermentation techniques could be divided into SSF, SHF, SSCF and CBF. SSF stands for Simultaneous Saccharification and Fermentation, whereas SHF is an abbreviation for Separate Hydrolysis and Fermentation. Both techniques allow yeast to utilize hexose fermentation (6-carbon sugar) under anaerobic conditions to produce ethanol. Accumulated ethanol is distilled after completed fermentation. The conventional SHF could be described as follows; firstly there is the initial pretreatment in which the lignocellulosic matrix is broken down, and then follows the enzymatic hydrolysis, which depolymerizes cellulose into glucose, after that the slurry is filtered and the sugar-rich fraction is transferred to the fermentation, where it is fermented into ethanol, normally with *S. cerevisiae* as the fermenting organism. Finally, there is the distillation/dehydration step, in which ethanol is extracted [12].

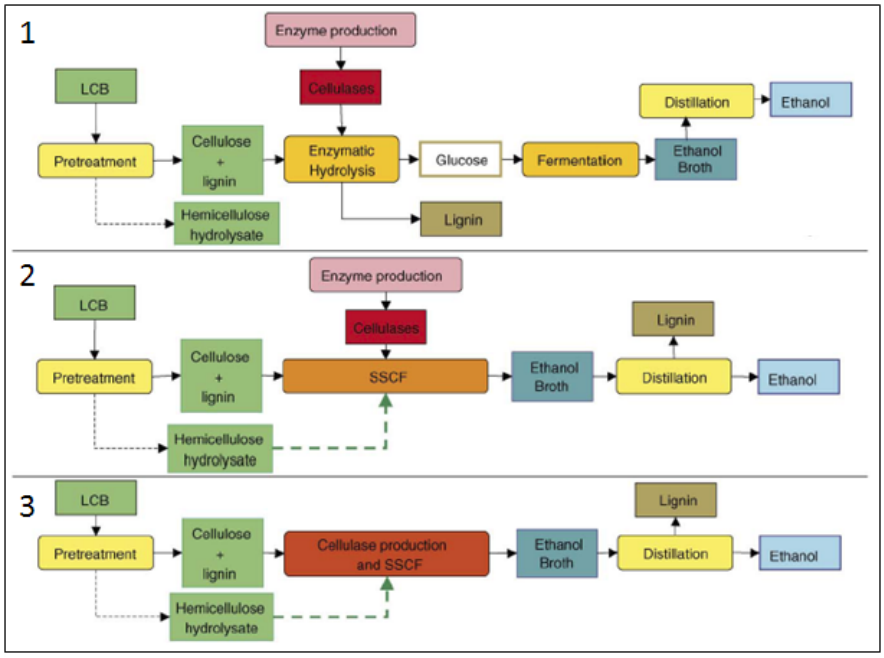

Figure 7. *Flow diagram 1 shows the conventional SHF process for producing ethanol from Lignocellulosic biomass (=LCB); flow diagram 2 shows the Simultaneous Saccharification and Co-Fermentation process (= SSCF) of hexoses and pentoses. And finally flow diagram 3 shows the Consolidated BioProcessing (=CBP), where the enzymes needed for hydrolysis are produced by the fermenting organism* [12].

2.5.1 Advantages/ disadvantages with SSF /SHF

The advantages of SSF compared to SHF are a simpler design, an extra process step is not needed, and there really is no product inhibition. One disadvantage with SSF is that nitrogen in the fermenting culture remains associated with the solid fraction and will thus be incinerated together with the solid residues, which causes formation of NO_x-gases. In SHF, the yeast can instead be re-circulated and the hydrolysis temperature is better optimized. There are also combinations of SSF and SHF available.

2.6 Metabolic pathways in yeast

Sugars such as glucose, fructose, mannose and other sugars are used by the fermenting organism as a carbon and energy source. Ethanol is produced under anaerobic conditions. A high yield of ethanol is the result of a successful fermentation. An important parameter is the amount of accumulated glycerol, which is either produced as the result of high osmotic stress or formed as a side-effect of biomass production.

In addition to the hexose related metabolism presented below in figure 8, fermenting organisms could also acquire pentose fermentation through genetic modification. In this context there are two main pathways to consider. The fungal type pathway uses two enzymes, *xylose reductase* and *xylitol dehydrogenase* with xylitol produced as an intermediate to produce D-xylulose. The inserted genes give the yeast the ability to overcome the problem of an unbalanced co-factor requirement. Both bacterial type pathway and fungal type pathway convert the pentose sugar D-xylose into D-xylulose.

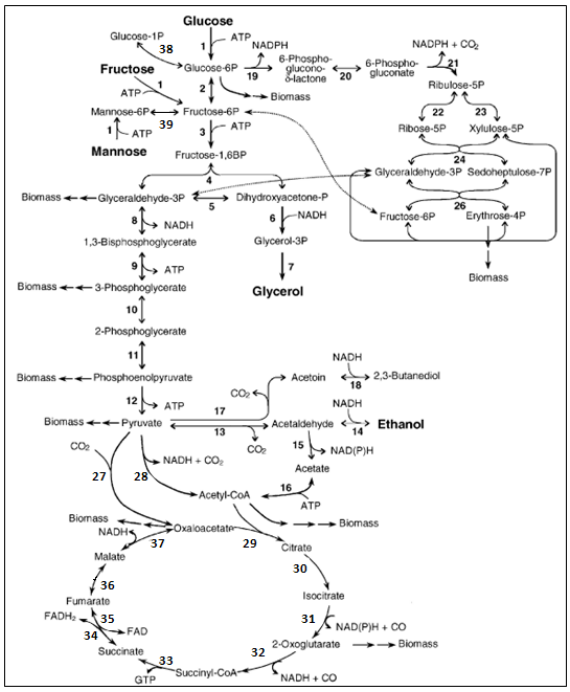

Figure 8. *Metabolic pathways in S. cerevisiae including the glycolysis sugar assimilation during anaerobic fermentation. The osmolyte glycerol is produced along with ethanol during fermentation* [13].

2.7 Optional fermenting organism

Traditional *Saccharomyces cerevisiae* (=Baker´s yeast) is a well characterized robust ethanol tolerant and ethanol producing organism. However, only hexoses are metabolized by the unmodified yeast strains [14].

Furthermore, *Zymomonas mobilis* has a potentially higher productivity of ethanol and lower biomass accumulation compared to *S.cerevisiae* but is more sensitive towards inhibitors. *Z. mobilis* is quite easy to modify genetically, but is currently only used as a hexose fermenting organism [15].

Moreover, there are bacteria such as *Escherichia coli*. *E. coli* is very well characterized indeed, but has in comparison to *S. cerevisiae* faster accumulation of biomass and relatively low ethanol production as well as a much higher sensitivity towards inhibitors [16].

There is also the *Mucor indicus*, which is a filamentous fungus with high tolerance towards ethanol and has a high yield of ethanol versus substrate. It can also metabolize five carbon sugars to some extent. The major drawback is that *M. indicus* is filamentous, which in turn leads to increased viscosity when the filaments are intertwined into a thick matrix [17].

In addition, there is also *Pichia stipidis*. *P. stipidis* is a hexose and pentose fermenting yeast but is bad for industrial purposes. Genes from *P. stipidis* for pentose fermentation has been transferred to Baker´s yeast, thus enabling a new robust strain competence of pentose fermentation [18].

2.8 The yeast strains Ethanol Red and a pentose fermenting strain

In this master thesis, two strains of *S. cerevisiae* were used during experimentation. Firstly, there is the Ethanol Red and secondly there is the pentose fermenting strain.

2.8.1 Ethanol Red

Ethanol Red is a developed strain of *S. cerevisiae* with excellent ethanol tolerance especially developed for the ethanol industry. The strain is however not competent to perform pentose fermentation. Characteristics displayed by the strain are higher cell viability during high gravity fermentation at elevated temperature (35°C), which results in lower cooling costs. Yields of 0,48 g/g ethanol and a final ethanol concentration of 18% v/v have been reported by the supplier Fermentis, a divison of S. I. Lesaffre [19].

2.8.2 The pentose fermenting strain

Recent research has resulted in a strain with genes capable of conversion of practically all hexoses as well as pentoses in biomass into ethanol. This is performed by insertion of bacterial genes for the enzyme *xylose isomerase* into yeast. This bacterial type pathway is then over expressed. The *xylose isomerase* is in addition assisted by another enzyme, *aldose 1-epimerase*, which increases the conversion rate between the xylose anomers β-D-Xylopyranose and α-D-Xylopyranose even further. Furthermore, the non-oxidative part of the pentose phosphate pathway is upregulated by over expressing several other enzymes such as; *xylulokinase*, *ribose-5-phosphate isomerase*, *transaldolase* and *transketolases*. All these enzymes ensure a fast metabolism of D-xylulose towards the glycolytic pathway via the intermediates Glyceraldehyde-3-phosphate and Fructose-6-phosphate [20].

2.9 Scandinavian approaches in Bio-refining

In Scandinavia there is a great demand for utilizing the vast resources of lignocellulosic readily abundant raw material via bio-refining. Currently, three different approaches in bio-refining are successfully emerging. The first is SEKAB E-technology, which is developing a technology that aspires to convert wood chips into ethanol as the main product. Secondly, there is Lignoboost, which tries to complement an existing conventional pulp mill, to extract the lignin from Black liquor. And thirdly, there is Borregaard Lignotech, which focuses on the Lignin-fraction to make various lignosulphonates, in addition to specialty cellulose products.

2.9.1 SEKAB E-technology, Örnsköldsvik, Sweden

At SEKAB E-Technology in Örnsköldsvik, Sweden, technology is developed to produce cellulosic ethanol from both hardwood and softwood. SEKAB´s research is based upon decades of various testing of process parameters, with Etanolpiloten at Örnsköldsvik as the current platform of development. Experience accumulated through Etanolpiloten encompass more than 29000 operative hours, since it was taken into operation in 2005. SEKAB E-Technology has received funding from both the Swedish Energy Agency and the European regional development fund [21].

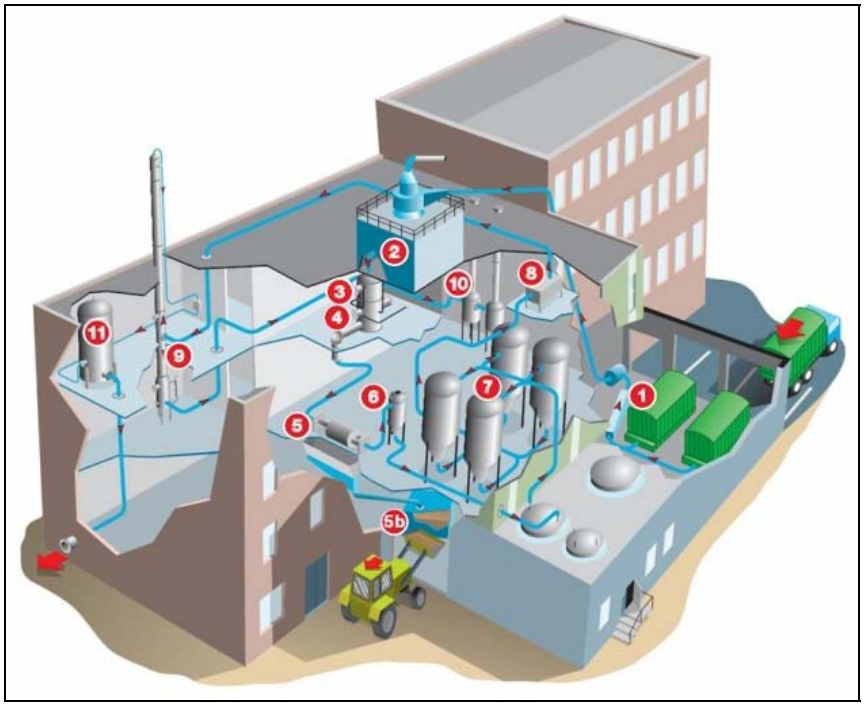

Figure 9. SEKAB´s Etanolpiloten. 1. *Intake, material is screened to remove large particles;* ***2.*** *Steaming, is used to preheat material and to remove air;* ***3.*** *Pre-saccharification, hemicellulose is leached out with acid at 170-200°C;* ***4.*** *The cellulose reactor, where cellulose is decomposed with acid at 200-300°C, followed by a cleavage process into soluble sugars;* ***5.*** *Membrane filter press, the lignin is filtered away. (If SSF is used, this stage could take place after stage 7);* ***5b.*** *The solid lignin, is removed;* ***6.*** *Detoxification, which removes inhibitory substances;* ***7.*** *Fermentation, sugar solution is fed to tanks kept at 35°C, enzymatic hydrolysis can also be carried out at this stage;* ***8.*** *Yeast separator, reuse of yeast from mash;* ***9.*** *Distillation, the distilled ethanol vapour is collected at the top of the distillation column, while stillage at the bottom of the column is discharged;* ***10.*** *Evaporation, after ethanol has been extracted, attention is given the stillage, which contain both liquid and solid fractions. These are concentrated through evaporation and then incinerated to produce heat. Process water streams undergo biological wastewater treatment before discharged;* ***11.*** *Product tank, ethanol is kept in large tanks before transport* [22].

2.9.2 LignoBoost at Bäckhammars Bruk, Sweden

At Bäckhammars Bruk, Sweden, currently operated by Innventia, the Lignoboost demo plant demonstrates a value added product biorefinery of black liquor into high purity lignin to be used as fuel additive in a lime kiln or to be sold for other applications. Since most pulp mills in Sweden are fairly similar to the facility in Bäckhammar it is appropriate to see how a bio-refining approach can complement an already established industry [23].

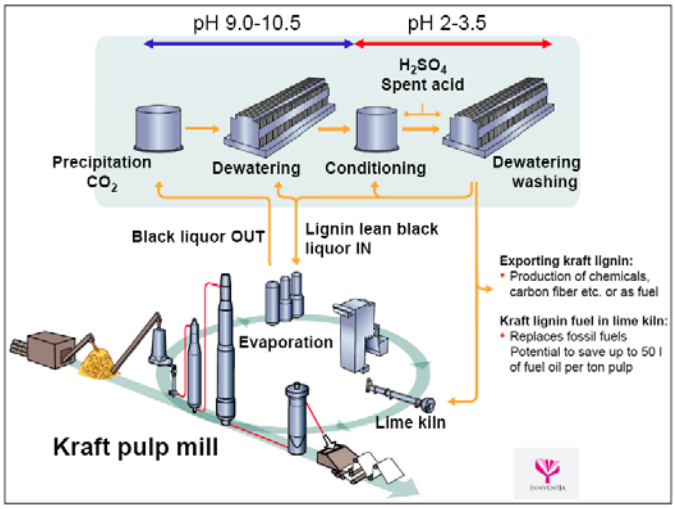

Figure 10. *LignoBoost process added to a conventional Kraft Pulp Mill at Bäckhammars Bruk, Sweden* [24].

2.9.3 Borregaard Lignotech at Sarpsborg, Norway

At Borregaard Lignotech, Norway, a new pilot plant is planned to demonstrate the potential of the newly patented BALI-process. The BALI-process is a sulphite based pre-treatment. Borregaard Industries claims to be a leading supplier of speciality cellulose as well as the global leader in high performance lignin derived chemicals. Further, Borregaard is the only producer of the flavour sweetener vanillin ($C_8H_8O_3$) from lignocellulosic raw material. Lignocellulosic bio-ethanol has been produced by Borregaard since 1938, and current production is approximately 20000 m^3 annually. Borregaard LignoTech lists the most popular industrial applications and functional uses for their lignosulphonate as follows; Binding Agent, Emulsion Stabilizers, Dispersing Agent, Extrusion Aids, Dust Suppressant, Retarders, Crystal Growth Modifier and Rheology Control [25].

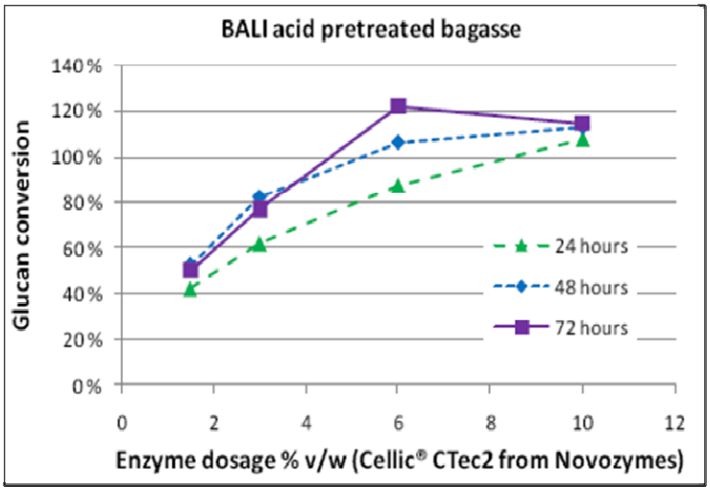

Figure 11. *The effectiveness of the enzyme Cellic Ctec2 in the BALI-process. Operation parameters were 6,3 % glucan loading, dry solids were 9,2%, Temperature was 50°C and the flasks was kept at 200 rpm in a shaking incubator. 50 mM Sodium citrate buffered around pH 5, Total reaction mass was 50 g in 100 mL flasks, and 0,01 % NaN_3 was added for microbial control. Enzyme producer Novozymes comment the results above as follows; "This is probably among the best 10-15 % of all results we have seen"* [25].

3. The Concept

The concept in this master thesis is to combine the cheap environmentally friendly pre-treatment of biomass performed by PLET, with enzymatic treatment and fermenting organisms in SSF or SHF on the cellulose and sweet liquor fraction, in order to produce a competitive next generation lignocellulosic ethanol.

3.1.1 A description of PLET and the patented process.

At present, PLET is an independent Canadian "Family and Friends"-sized business, and is thus considered as small company. The organization consists of the owners, consulting representatives and business relations managers. Current operations are carried out at a small demonstration plant in Canada. The company has been registered for about 6-7 years.

PLET is currently in the difficult process of leaping from lab and demo scale into full industrial scale. PLET is by far not unique; there are thousands of other recently started companies all over the world facing the very same challenges. What really catches attention is the way, in which PLET approaches one of the most difficult tasks in bio-refining. PLET provides a novel and innovative way of solving one of the toughest problems in bio-refinery. That is, the separation, fragmentation and purification of the complex biomass, into three high grade commercial products, with less generation of unwanted by-products, while also keeping the costs at a minimum [26].

Seen in figure 12, is a PFD (=Process flow diagram) of the patented technology from PLET. In brief words the process is described as follows. First the biomass is soaked in dilute nitric acid and then churned through an auger mechanism into a bioreactor where the nitric acid is evaporated and re-circulated. The cooked mesh is then transferred to a digester where the cellulose pulp is separated with alkaline treatment whereas the black liquor undergoes precipitation to separate the lignin as a dry product. The remaining sweet liquor could then undergo fermentation by Torula yeast (=*Candida utilis*) into unicellular protein [27].

The catalytic reactor process (=CRP), is performed by PLET in a continuous and batch system, in which lignocellulosic material (=wood chips, saw dust or other waste biomass) undergo acid catalyzed hydrolysis by dilute nitric acid. The impregnated wood chips are partially depolymerised from the lignin matrix when heated in the low pressure catalytic reactor. After that, follows distillation, condensation and almost complete recovery of dilute nitric acid. After the CRP, cellulose pulp is separated from the black liquor by an alkaline solution (=NaOH). The obtained black liquor is pumped to a separation tank to precipitate lignin and sweet liquor through filtration. The final step is to dry the lignin, while the sweet liquor is fermented by Torula yeast (=*Candida utilis*) into unicellular protein [26]. It is interesting to see if the process Company X provides, also could offer the solution to make next generation of cellulosic ethanol from waste biomass.

The lignin, extracted from the process is given extra attention according to PLET, since it has such high purity. Thus, it would be a potential candidate for a lot of new and interesting applications. PLET´s lignin is stated to have unique properties, which include high molecular weight and water solubility, to mention but a few. This extraction is possible thanks to the mild CRP, which uses low pressure, low temperature and not so harsh chemicals. While the lignin must be regarded as the main product, the cellulose fraction extracted and separated through the process is considered to be of standard commercial grade cellulose pulp.

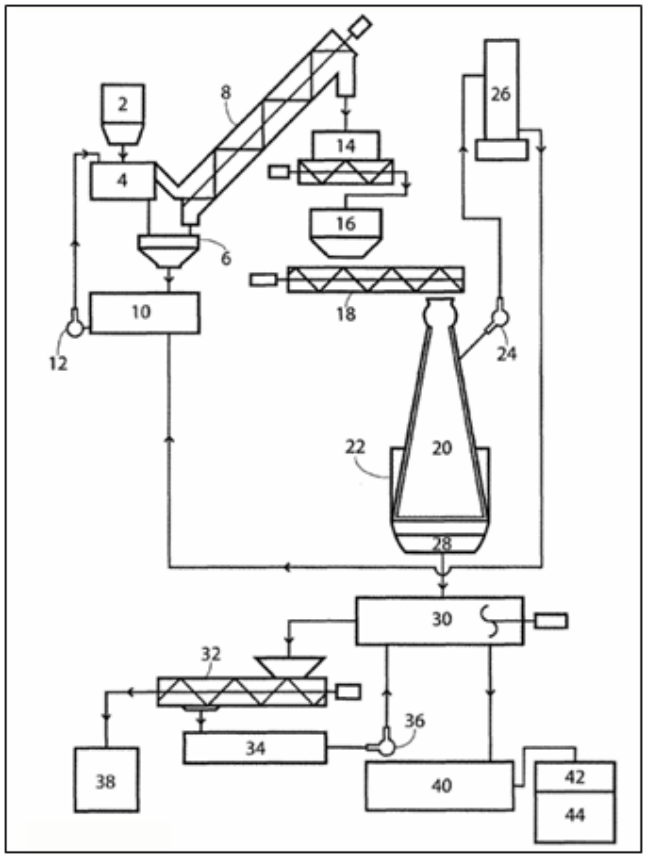

Figure 12. *A PFD (=Process flow diagram) of PLET patented technology, which incorporates a continuous and batch system to treat biomass in a closed loop. Raw material (=wood chips) are feed from a storage [2] over to impregnation chambers [4] along with dilute nitric acid from a solution tank [10]. After a soaking time the contents are transferred to a heated, low pressure reactor [20] by auger mechanisms [8]. After this the mesh [28] is treated with alkaline solution in a digester [30]. Evaporated impregnate and nitric acid and/or ammonium hydroxide is recovered via an absorption tower [26] and recycled back to the solution. The mesh is first heated then cooled in the alkaline treatment to separate the cellulose pulp [38] from black liquor. The black liquor is transferred to a lignin tank [40] in which the lignin is cooled and precipitated through filtration [42]. The lignin is dried and the remaining sweet liquor is ready for fermentation [44] into unicellular protein by Torula yeast. The unicellular protein could then be marketed as nutritious yeast. Depending of the intended results, the extracted fractions of cellulose, lignin and sweet liquor require extensive washing* [27].

According to statements given at PLET´s homepage; "For every 2,2 tons input of wood chips, the process produces 1,00 ton of cellulose, 0,42 tons of lignin and 0,78 tons of sweet liquor. After fermentation the sweet liquor is converted to 0,25 tons of protein." The prospect is to see if the cellulose and sweet liquor fractions could be used to cellulosic ethanol [26].

3.1.2 Sweet liquor, the by-product of dilute nitric acid pulping

The sweet liquor extracted from dilute nitric acid pulping contain more or less all the other chemical compounds not separated as pure cellulose and pure lignin from the original raw material. One way of making something valuable out of this diversified and complex mixture is to let Torula yeast (*Candida utilis*) grow on it in order to produce unicellular protein for animal food supplements. This sturdy robust yeast metabolizes almost everything of the otherwise toxic and inhibitory chemical compounds found in the extracted brown coloured sweet liquor.

Torula yeast has excellent nutritional properties, since it has such high nucleotides content, in particular RNA (ribonucleic acid). This makes Torula a good source for pet foods, especially for cats, but it is also frequently used as feed supplement to livestock in general. Furthermore, the Torula has a clean flavor profile, compared to the sometimes bitter taste of ordinary Yeast extracts from Baker´s yeast (=*Saccharomyces cerevisiae*), which makes torula useful as a flavor enhancer in animal food [28].

3.1.3 Advantages of the PLET concept

There are a number of arguments for choosing the PLET approach to process waste biomass. First of all, the starting raw material could be wet, since water takes part in the soaking pre-treatment with dilute nitric acid in the acid catalysed hydrolysis. It is generally regarded as bad water economy to dilute the raw material in conventional pre-treatment, but a wet starting material is actually preferable in the CRP-process. It is basically a fairly simple hydrolysis technology, which is performed at a low temperature and pressure along with a low input of energy to run the process. Only dilute acids and bases are used, thereby reducing raw material costs and unnecessary degradation of final products. In addition, usage of dilute acids and bases reduces the wear and tear on equipment used. The dilute nitric acid catalyst is recovered in a closed loop, which makes the processing almost pollution free.

Furthermore, the CRP generates commercial grade products such as high yield of α-Cellulose, native unique Klason lignin along with sweet liquor appropriate for a unicellular protein via fermentation of Torula yeast (=*Candida utilis*). The international EPA (EPA=Environmental Protection Agency) carbon dioxide pollution credit system ensures extra revenues, for implementation of a factory using CRP. Last but not least, CRP is flexible, since it could use any vegetation and/or waste biomass [27].

3.1.4 Disadvantages of the PLET concept

However, there are also some disadvantages that need to be addressed regarding the CRP. This is especially relevant when dealing with a new technology, which has not been put into full scale production yet. It is hard to compare the actual advantages of dilute nitric acid pulping to conventional pulping, since it has not been done before, at least not in the way PLET does it. Today there is no data apart from PLET´s own research supporting the approach to use nitric acid in pulping instead of sulphuric acid or other methods to extract high purity lignin and celluloses.

CRP offers another way of processing a lot of different raw materials, leading to three main products, each with their own specific value, all depending on oil price and commercial availability on a global market. So, the size and design of a future full scale processing unit must be made both according to customer specifications, and expected demands of the global market [27].

4. Technical and economical aspects of lignocellulosic ethanol

The technical and economical aspects of lignocellulosic ethanol could be described with the commercial flowsheeting programme Aspen Plus. The cost of major process equipment could be estimated by Icarus Process Evaluator (=IPE) from Aspen technology. Another alternative is to use computer software like Superpro for the technical layout of a process design and use Capcost to estimate the investments necessary if designing a large scale process plant. In this way it is possible to estimate the flow rate economy, its composition and energy flows for all processing streams.

A satisfactory concentration of fermentable sugars would be around 80 g/L or higher to support an industrial implementation, in addition the biomass yield during cultivation should be 0,5 g/g fermentable sugars. Ethanol must be concentrated in a distillation step consisting of stripper columns and a rectification column. The degree of distillation depends on how much ethanol could be concentrated during fermentation. It is generally regarded as "bad water economy" to add water during the processing since it has to be removed in the distillation step. In general, SSF:s has a better "water economy" than SHF:s [29]. It is however impossible to get accurate figures of what everything would actually cost, since prices of both equipment, raw materials, chemicals, utilities and other cost varies a lot depending on what amounts of quantities that are processed and current world market prices on bulk volumes [29].

Raw material		
Salix	555	SEK/dry metric ton
Corn stover	497	SEK/dry metric ton
Spruce	528	SEK/dry metric ton
Co-product income		
Solid fuel	185	SEK/MWh
CO_2	0.03	SEK/kg
Chemicals		
SO_2	1.5	SEK/kg
NaOH (50%)	1.5	SEK/kg
NH_3 (25%)[a]	2.0	SEK/kg
H_3PO_4 (50%)[a]	5.0	SEK/kg
Defoamer	20.0	SEK/kg
$(NH4)_2PO_4$[b]	1.5	SEK/kg
$MgSO_4 \cdot 7H_2O$[b]	4.4	SEK/kg
Molasses	1.0	SEK/kg
Enzymes	19.0	SEK/10^6 FPU
Utilities		
Electricity	300	SEK/MWh
Cooling water	0.14	SEK/m^3
Process water	1.4	SEK/m^3
Other costs		
Labour	600 000	SEK/employee/year
Insurance	1	% of fixed capital per year
Maintenance	2	% of fixed capital per year

[a] Chemical used in wastewater treatment.
[b] Chemical used as nutrient in SSF.

Figure 13. *Economic evaluation of three different feedstocks of lignocellulosic material, (Salix = Hardwood, Corn stover = biomass waste (herbaceous angiosperms) and Spruce = Softwood) as well as chemicals chemicals and other requirements needed, done by Department of Chemical engineering at Lund University. SEK is the currency in Sweden (1 SEK ≈ 0,09 Euro). Calculated example is taken from a potential not yet constructed processing plant of 200000 tonnes dry weight annually. The raw material is steam pretreated with SO_2. Note the high enzyme cost in the calculation, which is substantially reduced today [29].*

The process economy benefits from larger scale, but it is not certain that it is economically feasible. Although abundant, biomass requires storage when transported; in addition it is not a homogenous material, which makes it harder to accumulate sufficient amounts of raw material to the production plant. Raw material cost contributes most to the overall production cost, while the ethanol yield is the most important parameter for reducing the cost of ethanol production [29].

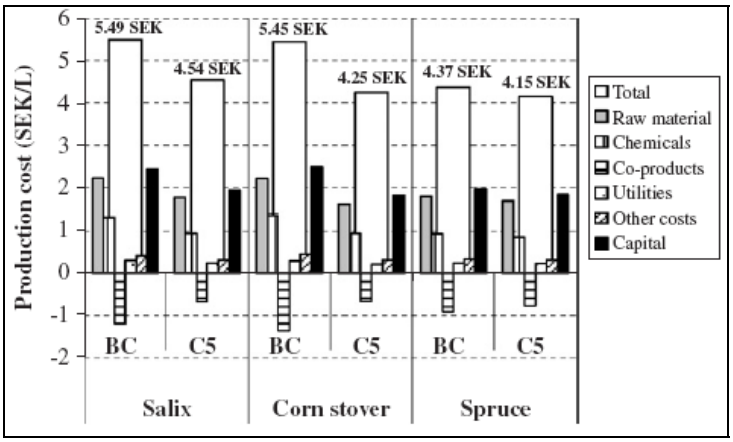

Figure 14. *Production cost calculation for the three cases (Salix = Hardwood, Corn Stover = biomass waste (herbaceous angiosperms) and Spruce = Softwood) done by Department of Chemical engineering at Lund University. All data refers to the same calculated example given in figure 17. BC refers to the base case while C5 refers to the pentose fermenting cases [29].*

The commercial viability of next generation lignocellulosic ethanol depends on; cost, availability and quality of the feedstock, pre-treatment technical process parameters and enzyme loading [30]. Finally, the product revenue could vary a lot due to world market demand. Still, the main indicator of commercial price of any product is the peak oil index.

In a study from 2003, the commercial prospects of lignocellulosic ethanol were evaluated by a comparison of the two major process configurations, SSF and SHF. The study was based upon softwood spruce. Ethanol production costs for the SSF and SHF were 4.81 SEK/L and 5.32 SEK/L or 0.57 USD/L and 0.63 USD/L, respectively. (1 USD = 8.5 SEK, in this study). SSF has lower production cost since the ethanol yield is higher than in SHF, the major drawback with SSF is the recirculation of yeast. The SSF could be improved by higher substrate loading and recirculation of process streams. If these arrangements were to be implemented, then their cumulative effect would result in a production cost of 3.58 SEK/L (0.42 USD/L) Seen in retrospect the decrease in production cost of lignocellulosic ethanol has been substantial over the last few years [31].

This study on the technical and economical aspects on lignocellulosic bio-refining into ethanol was however written before the pilot plant was inaugurated and the promised performance eventually turned out to be exaggerated. Despite the meager outcome of the pilot plant it is still interesting to analyze the approach. There are not that many studies that discuss both the technical and economical aspects at such early stage.

4.1 Business model canvas and the three phases envisioned

There are several ways available for formulating a business plan for a future company. This master thesis will use the simple business model canvas together with a timeline defined in phases, the most crucial topics and tasks that need to be addressed in the process of making a successful introduction of a small consulting bio-tech company. Some of the topics addressed in the business model canvas are obvious, but must nevertheless be clearly defined [32].

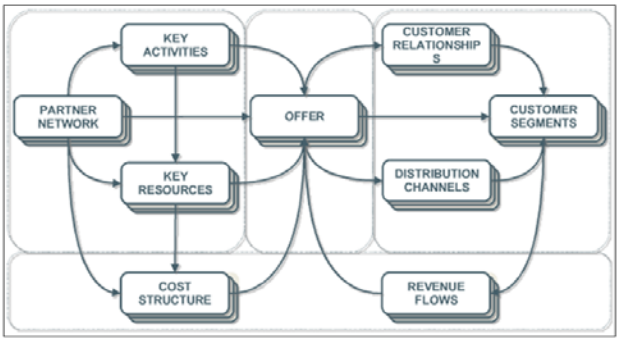

Figure 15. *Layout of the business model canvas, in which topic and tasks are defined and addressed with post-it tags on a large paper during a brainstorming session [32].*

4.1.1 Partner network, key activities and key resources

Partner Network, consists of PLET, SEKAB E-Technology, Högskolan i Borås, ESPIRA Inkubator, ALMI, Drivhuset, Innovationsbron, Innventia, Kommerskollegium, Svebio, Vinnova, Skogssällskapet Förvaltning AB. Affärsänglar (=Venture capitalists), Crowd funding [33] and/or Equity Crowd funding. And there are also the suppliers of enzymes (Novozymes) and yeast strains. *Key activities* would be marketing research of PLET products as well as displaying PLET technology at fairs, conferences and business meetings. Offer technical support for buyers and design applications of PLET process. Bio-tech research performed at Högskolan i Borås, thereby optimizing process parameters. *Key Resources* could be process data, support, licenses supplied by PLET, Högskolan i Borås. As well as experiments performed during master thesis and knowledge of how to handle equipment. A business network needs to be established and raw materials need to be assured. Other resources could be waste biomass produced at saw mills and paper pulping industries. Also there is a need to prepare proper conference material to support a business argumentation and put the technology in a current context as a cutting edge bio-refining alternative. Besides this, there may be necessary to specifically design computer software applications. Finally, there is also a possibility to utilize private capital and/or scholarship funding.

Customer relationships is to actively consult saw mills and paper pulp industries so that biomass waste could be turned into ”Value added products” on site, or collecting waste and take it to a future facility for processing. To consult industries involved in agricultural wastes thereby taking care of wastes like corn stovers, sugar cane bagasse, wheat straw et c, and textile lump of various origin (=cellulose rich substrates). Also, to consult and supply the chemical industry with high grade products from a demonstration facility for further synthesis. *Distribution channels* must transport raw material and processed products to and from facilities. This could be organized with trucks, trains or ships. Information, marketing and monetary transactions would be facilitated via internet. *Customer segments* include potential customers which would be saw mills and pulping industries.

The offer is to provide a non specific high grade separation of waste biomass into cellulose, lignin and sweet liquor, through an environmentally friendly pre-treatment step with dilute nitric acid pulping followed by enzymatic treatment and conversion into ”Value added products”. The commercial products are cellulose, lignin and sweet liquor or hemi-cellulose.

Revenue flows should come from consulting fees during the design/construction phase. Distribution of licenses; sold to partners using equipment designed by PLET. Revenues could also come from support agreements and equipment operations on site. Of course the major part of revenues would come in to the company when products such as specialty cellulose, ethanol, pure lignin, and unicellular protein for animal food are sold. *The cost structure* is important to consider. First of all a pilot plant must be purchased for demonstration purposes. License agreements must be made with PLET and an enzyme supplier. Other costs would encompass promotion, advertisements, business meetings, conference visits etc. The construction costs of a pilot plant and production plant are large and must be calculated with an estimated payback time. Equipment maintenance and estimated depreciation must be assessed. Administration, training of workers, salaries and social fees, taxes, permits etc. Design of future automation of processes at full scale production plant via PLC (=Programming Logical Control). Operation costs; transportation of raw material. Energy needed to run the processes. Chemicals; HNO_3, H_2O, NH_4OH, H_2SO_4, and HCl. Biological laboratory needed to cultivate large volumes of both enzymes and fermenting organisms like yeasts under licenses.

4.1.2 Economics of a future production plant

A production plant designed for processing 56 tons of wood chips per day of wood chips would generate annual revenues of ≈ 7500000 US dollars. The annual profit would be ≈ 2500000 US dollars, and capital cost (equipments) ≈ 5000000 US dollars, while the payback time on investment would be 2-3 years. The products are estimated to have the following values; 25 tons/day of pure Cellulose with a market value of 400-500 US dollars/ton, 10 tons/day of pure Lignin with a market value of 1000-1200 US dollars/ton and finally 21 tons/day of sweet liquor with a market value of 50-100 US dollars/ton [21].

4.1.3 Envisioned phases

Phase 1. First a master thesis of 30 ECTS must be written, in which samples from PLET pilot plant is analyzed in laboratory at Högskolan I Borås. Meanwhile a market analysis is performed, involving visits to conferences and business meetings. The prospect must be discussed with agencies and authorities and experienced people, as well as future investors such as Nyföretagarcentrum Sjuhärad, Banks etc. Time envisioned is six months. **Phase 2.** Involve the formation of a share holding company including study visits to PLET. There would be a need to purchase or lend/lease of 1st pilot plant. Personnel need to be hired to do tasks. A future factory would be designed in computer software such as Superpro or ASPEN Plus along with an economical calculation of estimated costs and incomes using CAPCOST. Marketing could be done on exhibitions, fairs and other events. Time estimated for these tasks are one year. **Phase 3.** The actual construction and supervision of a factory for production of lignocellulosic products must be done. The factory envisioned would employ about 20 persons. Supply lines need to be administrated, as well as even larger full scale production plants must be designed. A network needs to be established. And production needs to be optimized in order to reduce costs. If these tasks are successfully executed the company would expand to other sites in Scandinavia. Expected time for this would be at least ten years.

4.2 Technical and Customer oriented parameters to consider

There are many ways to estimate what is important to consider before launching a project in bio-refining. Below are two examples given of how these parameters/factors could be addressed and formulated as questions, which a future entrepreneur in bio-refining must be prepared to answer satisfactory. The technical and customer oriented parameters are to be considered. In addition, these parameters must be ranked and put into an international context.

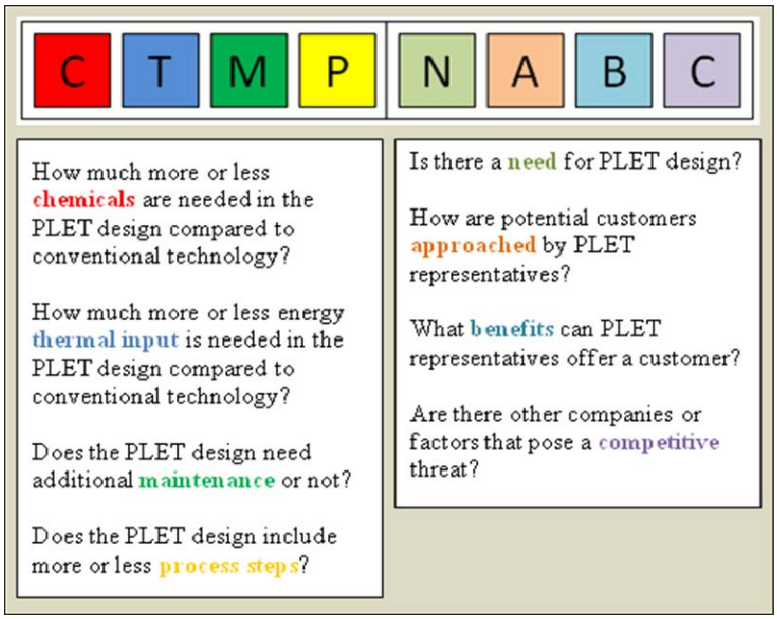

Figure 16. *Technical parameters are C = Chemical, T = Thermal, M = Maintenance and P = Process. Customer oriented parameters are N = Need, A = Approach, B = Benefit, C = Competition* [34].

Parameters to consider could be ranked after importance according to Lena Dahlman at Svebio.se. Starting with; economic framework, feedstock availability, financial markets and investment capital from banks, authorities and legislation, energy markets, process energy requirements, market saturation level, political stability and public acceptance [35].

5. Methods and materials

This section includes a description of the raw material, equipment used for experiments, as well as a more detailed description of the six conducted experiments.

5.1 Raw material

In experiment 1, dilute SO_2- pretreated birch slurry from SEKAB E-Technology was used. Samples from SEKAB E-Technology serves in this master thesis as a comparison since the dilute SO_2- pretreated birch slurry process is well documented and relatively close to commercial application. The approach during this project is to determine whether the presumably simpler process suggested by PLET is preferable compared to SEKAB E-Technology´s processing of biomass, due to lower cost and potentially environmental impact.

In experiments 2 to 6, samples from the pilot plant of PLET were used. Dilute nitric acid pretreated samples supplied by PLET were taken from different stages of the whole process. Within the scope of this project the washed cellulose fraction (WC), the unwashed cellulose fraction (UWC) and the sweet liquor (SW) were used for analysis and trials, while only minor attention was given the main product pure lignin. According to PLET, the lignin produced already is a commercial grade product. Hence focus was concentrated on determining if pretreatment suggested by PLET is sufficient to produce the next generation of lignocellulosic ethanol from softwood.

5.2 Equipment used during experiments

5.2.1 Biostat B-Plus fermentor

A Biostat B-Plus fermentor was used for SSF and SHF experiments. In addition, experiments performed in the Biostat B-plus fermentor was complemented with shake flask fermentations.

Parameters applied in experiments with Biostat B-Plus were as follows. The *pH*, was kept within an interval of 5,0 to 5,5 by addition of 1 M sulfuric acid (H_2SO_4) and/or 1 M sodium hydroxide (NaOH). The *temperature* was set to 50 °C to increase enzymatic activity in SHF, while lowered to 35 °C, during the subsequent fermentation. In SSF experiments, the temperature was set to 35 °C throughout the whole process. A *stirring speed* of 1200-1500 rpm was initially used in order to maintain satisfactory mixing (rpm = rounds per minute). However, the stirring speed was lowered to 400-500 rpm as soon as viscosity decreased sufficiently during the enzymatic hydrolysis. In shake flask experiments the stirring speed was set to 120 rpm.

Figure 17. *The Fermentor Biostat B-Plus, linked to a computer controlled interface for automatic monitoring and adjustment of stirring rate, temperature, pH and O_2-supply* [36].

5.2.2 HPLC-analysis

HPLC, high performance liquid chromatography, was used to determine concentrations of sugars and accumulated ethanol in collected samples. Computer software supporting HPLC analysis was EmpowerPro version 6.2. Two columns were used in experiments; the H-column (Aminex® HPX-87 H, 300 mm*7,8 mm) and the P-column (Aminex® HPX-87 P, 300 mm*7,8 mm) supplied from BioRad [37]. For the P-column samples, removal of sulphate was required before run in the HPLC. This was done by addition of $Ba(NO_3)_2$ to each sample, enabling easy separation of insoluble $BaSO_{4(s)}$.

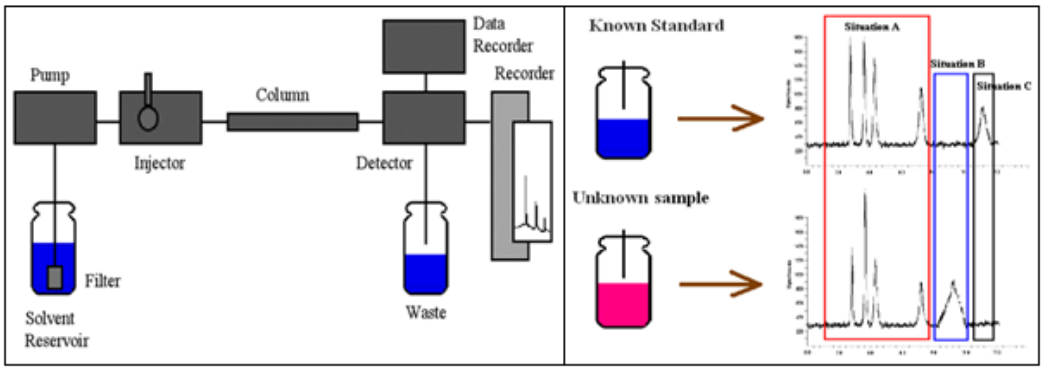

Figure 18. *Simplified structure of the HLPC equipment and how HPLC chromatograms could be interpreted. HPLC compares the retention time for samples and standards. Corresponding peaks are found (situation A), which means that there are the equivalent chemicals in both standard and sample. Concentration of chemicals in the sample equals to the concentration of chemicals in Standard *(peak area in sample/ peak area in standard). In situation B, there is a peak in the sample, but no peak at the same fraction in standard, which means that the sample contains a certain chemical not present in standard. In situation C, there is a peak in the standard, but no peak at the same fraction in sample, which means that the standard contains a certain chemical not present in the sample* [38].

5.2.3 Dry weight measurements

Dry weight measurements were determined by sampling of 5 ml hydrolysis or fermentation broth. Samples were transferred to glass tubes and centrifuged at 5000 rpm for 5 minutes and then washed with deionized water and dried in an oven overnight at 105 °C. The weight was measured and compared to the weight of the empty (dry) glass tube [39].

5.2.4 Enzyme kit

Glucose enzymatic kit uses the measurable UV-absorbance of NADH at 340 nm as a measurement of glucose content in a solution. The enzyme hexokinase converts glucose into Glucose-6-Phosphate assisted by ATP. Then the enzyme G6PDH catalyzes the reaction of Glucose-6-Phosphate and NAD^+ into 6-Phosphogluconate and the optically active NADH. The NADH contributes to an increase of absorbance measured by spectrophotometer at wavelength 340 nm, which on a molar basis is equivalent to the initially present glucose molecule [40]. Cell density was in some applications estimated with a spectrophotometer by measuring the optical density (OD) at 610 nm. Absorbance is compared to a standard from dry weight measurements and then recalculated to concentration in g/L [41].

5.3 Summary of conducted experiments

In Table 1, there is a brief description of the six different experiments performed. In the first five experiments, extracted samples were collected for HPLC analysis. These extracted samples were complemented with corresponding dry weight measurements in order to determine ethanol yield of processed raw material. Experiment 6 was a simple lignin dry weight / polycondensation estimation which purpose only was to analyze general characteristics.

Table 1. *Showing the different experiments performed in laboratory.*

	Raw material	***Procedure***	***Enzymatic treatment***	***Fermenting organism***
Experiment 1	*Birch slurry, (SEKAB E-technology)*	*SSF*	*Cellic Ctec2*	*Pentose fermenting strain*
Experiment 2	*Washed cellulose (WC), (PLET)*	*SHF*	*Cellic Ctec2*	*Ethanol Red*
Experiment 3	*Unwashed cellulose (UWC), (PLET)*	*SSF/SHF*	*Cellic Ctec2*	*Ethanol Red*
Experiment 4	*Sweet liquor (SL), (PLET)*	*SSF*	*Cellic Ctec2*	*Pentose fermenting strain*
Experiment 5	*Sweet liquor (SL), (PLET)*	*SSF*	*Cellic Ctec2*	*Pentose fermenting strain*
Experiment 6	*Pure lignin, (PLET)*	*Dry weight, Polycondensation*	-	-

A general outline of the mass flow modes in SHF and SSF are difficult to explain unless a graphical presentation is used, which preferably can be seen in figure 19 and 20.

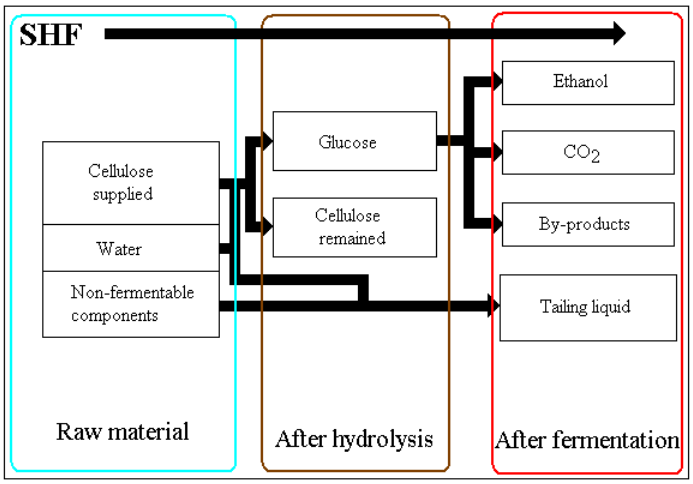

Figure 19. *SHF Mass flow mode*

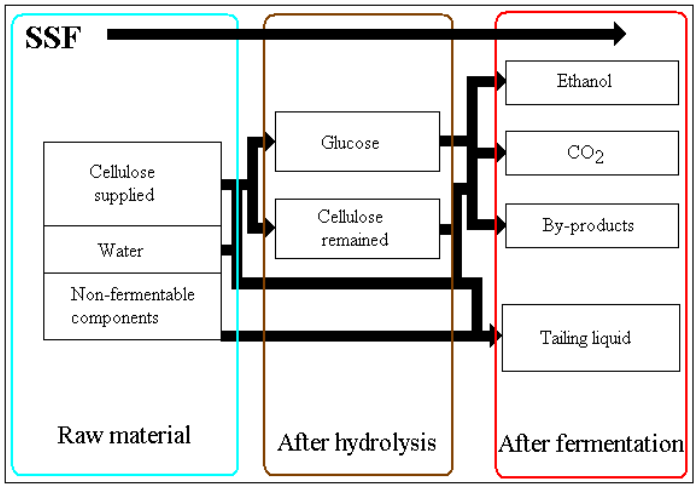

Figure 20. *SSF Mass flow mode*

5.4 Experiment 1

Firstly, 2000 mL glucose-xylose containing liquid medium (100 g glucose, 100 g xylose, 5,0 g peptone, 5,0 g yeast extract) was prepared. The pentose fermenting yeast was inoculated into a 100 mL medium containing 5,0 g glucose, 5,0 g xylose, 2,0 g yeast extract and 2,0 g peptone. At t = 0, the 4 mL of yeast suspension was added to medium. At t = 0 hours, the first addition of birch slurry 300 g was mixed with 20 mL 1 M NaOH in order not to expose the yeast culture to a pH shock. The pH was adjusted to 5,5. The total weight of the first addition of birch slurry to Biostat B-Plus was 321 g. Simultaneously at t = 0 hours, 20 mL Cellic Ctec2 enzyme was added. A second addition of (321 g) was prepared and added to the Biostat B-Plus at t = 8 hours. After 48 hours of cultivation, the volume was adjusted to 700 ml. At the time t = 53,5 hours the third birch slurry addition (321 g) was added. When the last sample was collected, fermentation stopped. All samples were centrifuged for supernatant extraction at (10000 rpm, 5 minutes) followed by storage in freezer until HPLC. Samples were extracted at t = 0; 2; 26; 53; 72; 80; 96 and 100 hours. See layout of experiment in figure 21.

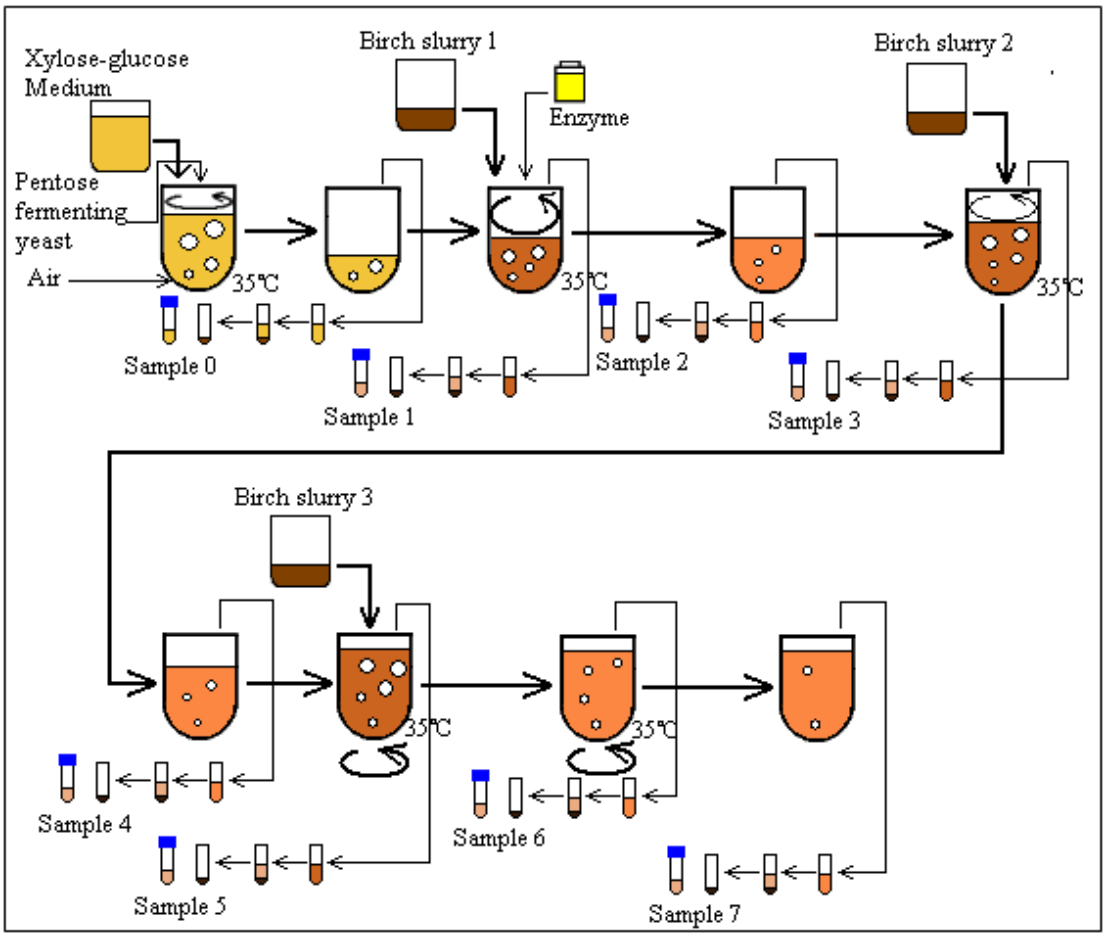

Figure 21. *The performed birch slurry fermentation. Three additions of birch slurry were added to the pentose fermenting yeast medium. Samples were extracted throughout the hydrolysis and fermentation process for HPLC and dry weight estimation.*

5.5 Experiment 2

From a wet yellow brown mesh of washed cellulose fibers 75 g of floccules were well mixed with 300 mL milliQ-water. Then pH was adjusted to 5,5 with 1 M sulfuric acid (1M). Slurry was after that transferred to Biostat B-Plus, which was autoclaved at 121 °C for 20 min, and cooled to 50 °C. The pH of the slurry was readjusted to 5,5. Water was added to the slurry until the viscosity was manageable. At t = 0 hours, 7 mL of enzyme Cellic Ctec2 was added and left for hydrolysis for 24 hours at 50°C. A second addition of 75 g slurry in 300 mL water was prepared and added to Biostat B-Plus at 25 hours. The hydrolysis continued until 49 hours until the third addition of slurry was made. The hydrolysis continued until 72 hours after which the Biostat B-Plus was cooled down to 35°C. At t = 95 hours, 10 g of dry Ethanol Red yeast was added to the Biostat B-Plus for fermention. The fermentation was stopped at the time t = 100 hours. Samples were extracted at t = 24; 48; 72 and 100 hours. See layout of experiment in figure 22.

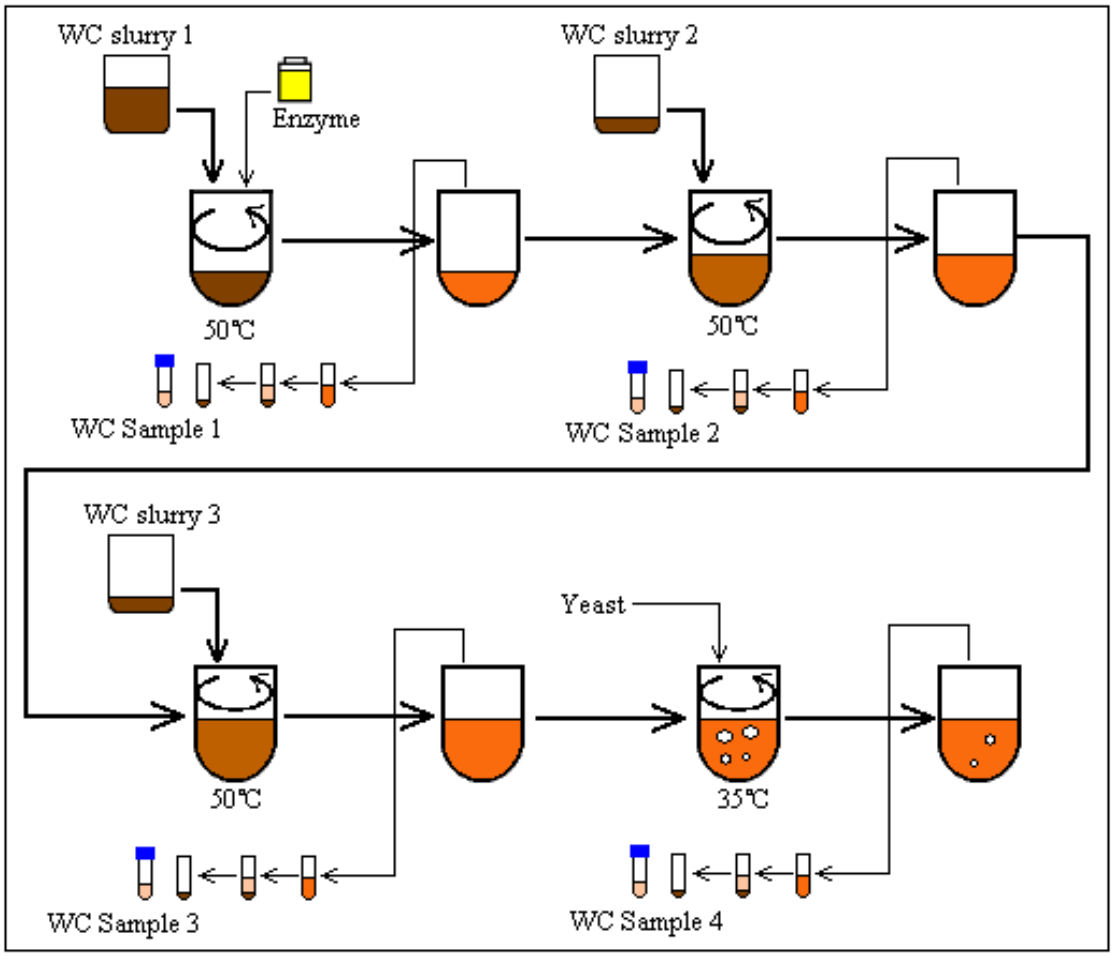

Figure 22. *Washed cellulose (WC) fermentation. Three batches of WC slurry were mixed with enzyme and hydrolyzed at 50°C. Yeast was added to hydrolyzed medium and fermentation was performed at 35°C. Samples were collected during hydrolysis and fermentation process.*

5.6 Experiment 3

From a compact cake of unwashed cellulose, 150 g was churned into smaller pieces and mixed in 300 mL milliQ-water. Then, pH was adjusted to 5,5 with 1 M sulphuric acid. Thus was the slurry prepared. Slurry was then transferred to the Biostat B-Plus fermentor and autoclaved at 121°C for 20 minutes, then cooled to 50 °C. The pH was readjusted to 5,5 and sufficient milliQ-water was added to Biostat B-Plus in order to enable stirring to a total volume of 1540 mL. Suspended solids (SS) concentration was 86,0 g/L. Then, 25 mL Cellic Ctec2 enzymes was added at t = 0 hours, which resulted in an enzyme concentration of 1,6 % starting hydrolysis. At 24 hours 150 mL of the slurry was extracted from the Biostat B-Plus to start fermentation in shake flasks A and B each given 75 mL of the slurry along with 10 g dry Ethanol Red yeast, labeled as 1FA and 1FB (1FA= first fermentation flask A). Flasks were left for 24 hours fermentation at 35 °C. At 48 hours, a second shake flask fermentation was started in the same way. Meanwhile, the hydrolysis continued in Biostat B-Plus. A second batch of slurry, 150 g unwashed cellulose, was prepared and added at 25 hours. A third batch of slurry was prepared in the same way and added at t = 49 hours. After extractions for a third shake flask fermentation at 71 hours, the Biostat B-Plus temperature was cooled to 35 °C. At 71 hours, 10 g dry Ethanol Red yeast, 10 mL Enzyme Cellic Ctec2 and 2 g ammoniumsulphate $(NH_4)_2SO_4$ was added to the Biostat B-Plus to start a fermentation, which ended at 120 hours. In parallel with the fermentation in Biostat B-Plus an additional shake flask fermentation was started. Samples were extracted at t = 0; 24; 25; 48; 49; 72; 95 and 120 hours. See layout of experiment in figure 23.

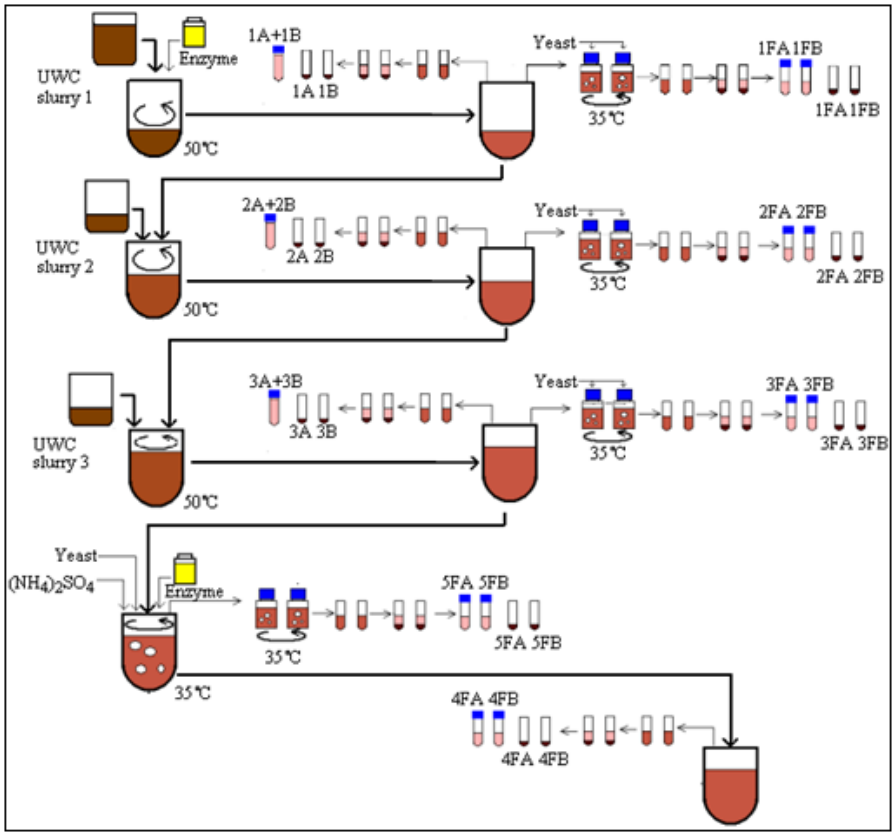

Figure 23. *The unwashed cellulose fermentation. Three batches of UWC slurry were mixed with enzyme and hydrolyzed. Five series of hydrolyzed slurry were collected and added yeast to ferment. Samples were collected during hydrolysis and fermentation process.*

5.7 Experiment 4

The sweet liquor is a dark brown liquid. The pH of sweet liquor is 3,2. Experiment 4 was a fermentation of differently diluted sweet liquor, fermented by pentose fermenting yeast. The experiment was duplicated in five dilution sets (50 ml/0ml = no dilution, 40 ml/10 ml, 30 ml/20 ml, 20 ml/30 ml, 10 ml/40 ml) all adjusted to pH= 5,0. The pH was adjusted to 5,0 with 1 M NaOH before addition of 2 g $(NH_4)_2SO_4$, 2 g KH_2PO_4 and 8 ml pentose fermenting yeast suspension to each bottle. The fermentation was performed at 35 °C, and 100 rpm for 72 hours. Samples were collected at 0 and 72 hours. See layout of experiment in figure 24.

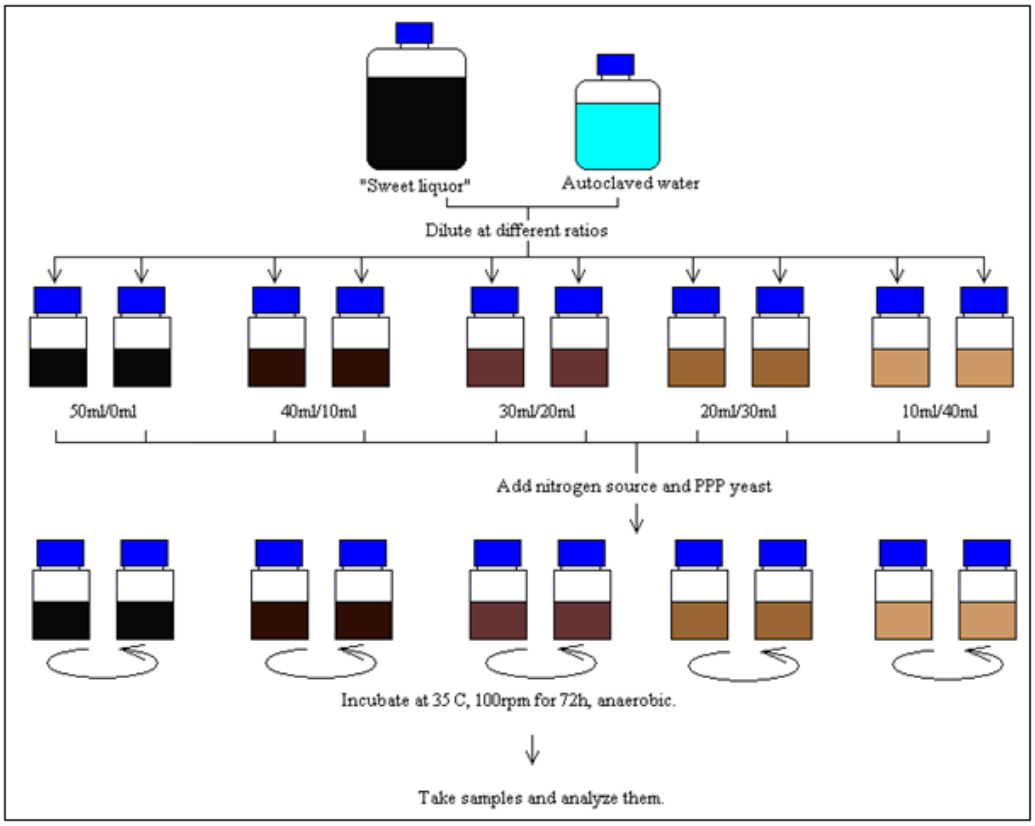

Figure 24. *A layout of experiment 4. Five sets of media were prepared from sweet liquor and autoclaved water at different dilutions. All series of media were mixed with an additional nitrogen source and pentose fermenting yeast as fermenting organism. Samples were taken after fermentation and were analyzed.*

5.8 Experiment 5

Experiment 5 was a fermentation of various concentrations of added yeast extract and cell concentration. Yeast extract levels were 0 g/L, 1,0 g/L, 5,0 g/L while pentose fermenting yeast cell levels were 0,5 g/L, 1,0 g/L, 1,5 g/L. The pH was adjusted to 5,0 with 1 M NaOH before addition of 2 g KH_2PO_4 and specific amount of pentose fermenting yeast cells and yeast extract according to the presentation seen in figure 25. The fermentation carries out for 72 hours at 35 ℃, 100 rpm. Samples were collected at t = 0 and 72 hours.

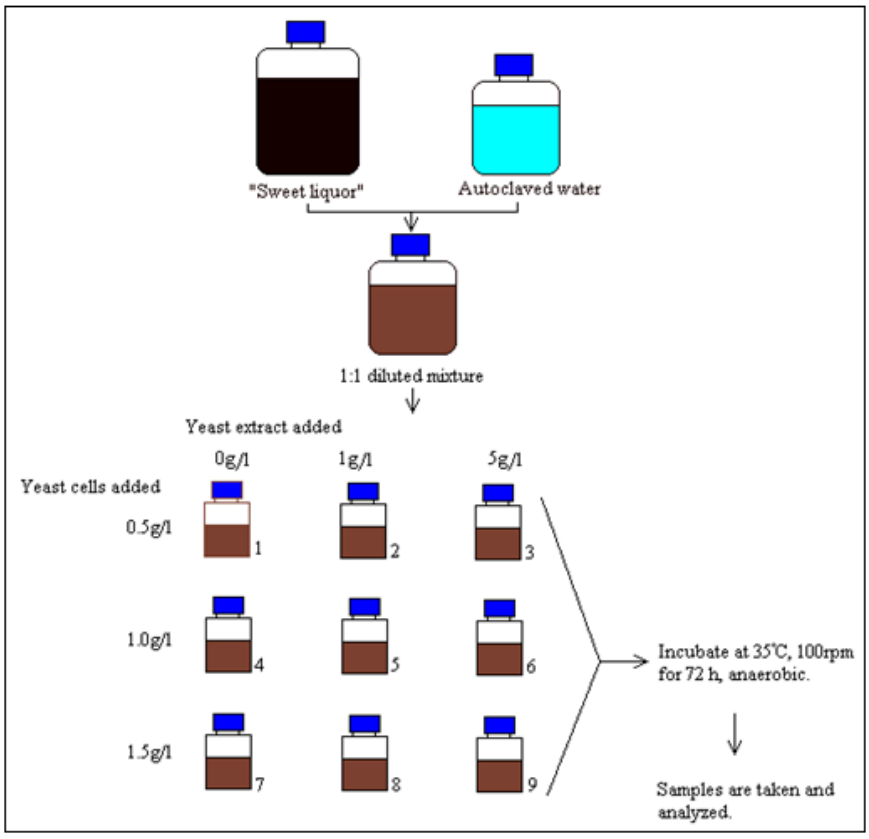

Figure 25. *Seen above is the experimental layout of experiment 5. A medium was prepared from sweet liquor and autoclaved water. This medium was separated into 9 bottles and yeast extract and different amounts of yeast cells were added. Samples were extracted and analyzed after 72 hours of fermentation.*

5.9 Experiment 6

In order to determine whether the lignin from Company X can be used as raw material for polyphenolic resin production or not, a polycondensation experiment was performed by complete mixing of 10 g lignin with 0,2 g $NaOH_{(s)}$ and 10 g furfural $(OC_4H_3CHO)_{(l)}$. The mixture was then incubated at 150 °C for 20 minutes, after which it was cooled to 20°C. The polycondensation was complemented with dry weight estimation [42].

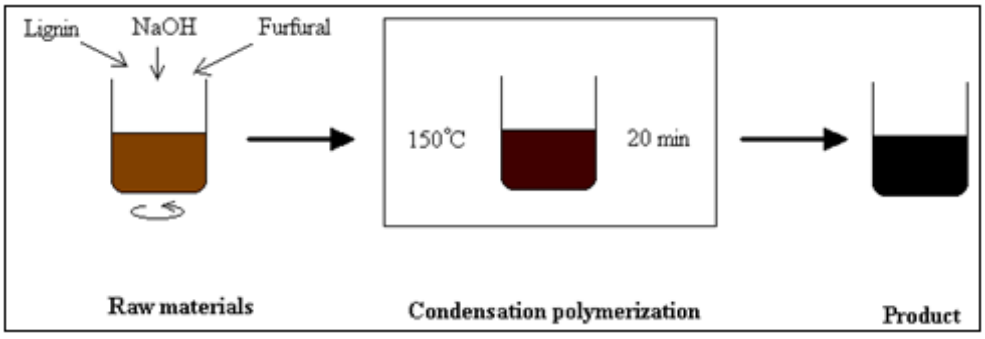

Figure 26. *A graphic presentation of the lignin polycondensation experiment.*

6. Results and Discussion

In this section, results from the six different experiments are displayed and discussed. Examples of calculations of dry weight, yield, cell density and glucose concentration are also included. All raw materials in lignocellulosic ethanol production can be classified into two components: fermentable and non-fermentable sugars derived from celluloses and hemi-celluloses, plus all other still remaining structural wood components. The fermentable part is a complex mixture, where cellulose can be considered as the major raw material component. In order to simplify the theoretical yield calculation it was assumed that the washed cellulose of PLET sample contained 100 % pure cellulose, which is a simplification.

The hardwood birch slurry with hexoses derived from cellulose and pentoses derived from hemi-cellulose from SEKAB E-Technology, in contrast to the pure cellulose from PLET, which has a simplified mass flow mode as follows.

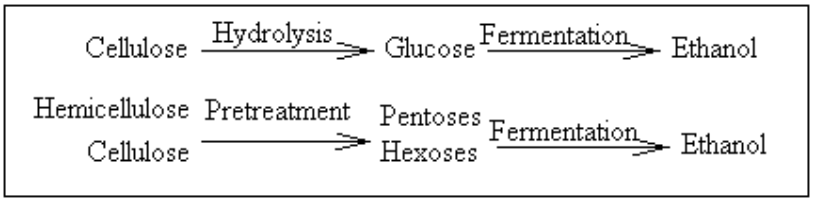

Figure 27. *The two steps, hydrolysis and fermentation in a SSF and/or SHF.*

Formulas used to calculate yields stoichiometrically was [m = n * *M*], [n = c * v] and [c_1*v_1 = c_2* v_2], where m = mass in gram, n = number of mol, *M* = molar mass in g/mol, c = concentration in g/dm^3 and v = volume in dm^3 or L. Dry weight percentage is expressed as the cellulose supplied plus non fermentable dry matter divided by the cellulose supplied plus non fermentable matter plus water. So, the dry initial raw material could be considered as cellulose supplied plus non fermentable matter.

6.1 Yield calculations (theoretical versus actual yield)

Reaction 1 is cellulose into ethanol stoichiometrically balanced net reaction, whereas reaction 2 and 3 show simplified balanced reactions of hemicelluloses into ethanol under aerobic and anaerobic conditions respectively if no consideration is taken to biomass formation.

Reaction 1: $(C_6H_{10}O_5)_n + n\ H_2O \rightarrow n\ C_6H_{12}O_6 \rightarrow 2*n\ C_2H_5OH + 2*n\ CO_2$
Reaction 2: $(C_5H_8O_4)_n + n\ H_2O \rightarrow n\ C_5H_{10}O_5 + 0{,}5*n\ O_2 \rightarrow 1{,}5*n\ C_2H_5OH + 2*n\ CO_2$ [43]
Reaction 3: $(C_5H_8O_4)_n + n\ H_2O \rightarrow n\ C_5H_{10}O_5 \rightarrow 1{,}67*n\ C_2H_5OH + 1{,}67*n\ CO_2$ [43]

Table 2. *Showing the molar weights of molecules that take part in hydrolysis and fermentation.*

$M_{(Cellulose\ unit)}$ = 162 g/mol	$M_{(Water)}$ = 18 g/mol	$M_{(D\text{-}Glucose)}$ = 180 g/mol
$M_{(Hemicellulose\ unit)}$ = 132 g/mol	$M_{(D\text{-}Xylose)}$ = 150 g/mol	$M_{(Ethanol)}$ = 46 g/mol
$M_{(Carbondioxide)}$ = 44 g/mol	$M_{(Oxygen)}$ = 32 g/mol	

In a SHF both the hydrolysis and fermentation must be considered as two steps;

Theoretical hydrolysis yield = 180 / 162 = 1,11 (g glucose / g cellulose)
Theoretical fermentation yield = (2 * 46) / 180 = 0,51 (g ethanol / g glucose)
Theoretical total yield = (2 * 46) / 162 = 0,57 (g ethanol / g cellulose)

Hydrolysis yield = Glucose / Cellulose supplied
Fermentation yield = Ethanol produced / Glucose
Actual yield = Ethanol produced / Cellulose supplied
Percentage yield = Actual yield / Theoretical yield

Whereas theoretical yield calculations are simplified in a SSF, where the total reaction is considered as;

Theoretical total yield = 2*46 /162 = 0,57 (g ethanol / g cellulose)
Actual yield = Ethanol produced / Cellulose supplied
Percentage yield = Actual yield / Theoretical yield

6.2 Experiment 1: Birch Slurry SSF

6.2.1 Results of Experiment 1

The birch slurry is a red-brown pasty substance with a pH at 2,5. The birch slurry SSF involved three sequential additions (total amount added 900 g) of birch slurry to a pentose fermenting yeast medium along with 20 mL Cellic Ctec2 enzymes. In the dry solid measurement the cellulose fraction is marginal compared to free sugars. The total SS content, also known as the dry solid concentration was 185,8 g/L.

In all calculations presented below, the density ratio is approximated as 1 g = 1 mL. In the 700 mL start-culture there were substantial amounts of glucose, xylose and ethanol which cannot be neglected. These amounts have to be subtracted from the actual SSF performed;

Glucose: 0,6 g/L* 0,7 L = 0,4 g
Xylose: 27,2 g/L * 0,7 L = 19,0 g
Ethanol: 7,1 g/L* 0,7 L = 5,0 g

When the actual SSF was initiated to Biostat B-Plus, there were three separate additions of 300 g slurries plus 21 g NaOH, with dry solids content of 16 %. It is assumed that the solid fraction of the slurry contained 50 % cellulose. Consequently, the Biostat B-Plus received;

Dry solid weight: 3 * 300 * 0,16 = 144 g
Dry solid concentration: 144 / 1,6 L = 90 g/L
Glucose: (3,8 g/L * (0,7 L + 0,321 L) - 0,4 g) * 3 = 9,3 g
Xylose: (36,7 g/L * (0,7 L + 0,321 L) - 19,0 g) * 3 = 44,4 g
Cellulose: 144 g * 0,50 = 72 g

According to HPLC data the final solution contained;

Glucose: 8,0 g/L * 1,6 L = 12,8 g
Xylose: 10,8 g/L * 1,6 L = 17,3 g
Ethanol: 44,4 g/L * 1,6 L = 71,0 g

Yield calculation of the ethanol produced and the productivity of birch slurry SSF requires that the amounts added from pre-culturing is subtracted. The total volume of the pre-culture plus the added slurry during the experiment was considered as 1,6 L, which includes an approximation for the volume lost during sampling. The theoretical fermentation yield of 0,51 g ethanol /g glucose cannot be assumed, at best a 90 % of theoretical yield could be expected as described below;

Ethanol from pre-culture: (0,4 g + 19,0 g) * 0,51 g/g * 0,90 = 8,9 g
Ethanol from slurry: 71,0 g - 8,9 g = 62,1 g
Actual total yield: 62,1g / 144 g = 0,43 g ethanol / g dry raw material
Ethanol from free sugar: (0,4 g + 19,0 g + 9,3 g + 44,4 g) * 0,51 g/g * 0,90 = 33,6 g
Ethanol from cellulose: 71,0 g - 33,6 g = 37,4 g
Cellulose consumed: 37,4 g / (0,9 * 0,57 g/g) = 72,9 g
Productivity: 62,1 g / (73 h * 1,6 L) = 0,53 g/h*L

Produced ethanol concentration: 37,4 / 1,6 = 23,4 g/L

Table 3. *The concentration of dry material and ethanol for the birch slurry SSF. Assuming that the ethanol production was based on complete consumption of free sugars (with 90 % of 51 % yield = 46%).*

	Dry raw material	Produced Ethanol	90 % of theoretical yield of ethanol	Free sugars added (xylose + glucose)	Free sugars remained (xylose + glucose)	Consumed cellulose
Concentration	185,8 g/L	23,4 g/L	75,5 g/L	40,5 g/L	18,8 g/L	82,5 g/L

Amount of free sugars added to the system was 36,7 g/L xylose + 3,8 g/L glucose, including pentoses and hexoses. The produced ethanol was 44,4 g/L at 73 hours when the experiment was ended. Assuming that the ethanol production was based on complete consumption of free sugars (with 90 % of 51 % yield = 46 %). Since there is 23,4 g/L produced ethanol in the end sample then the initial raw material must have contained at least 82,5 g/L of cellulose. The actual total yield is calculated in "g ethanol / g dry raw material". Then the actual total yield is 0,43 g ethanol / g dry raw material.

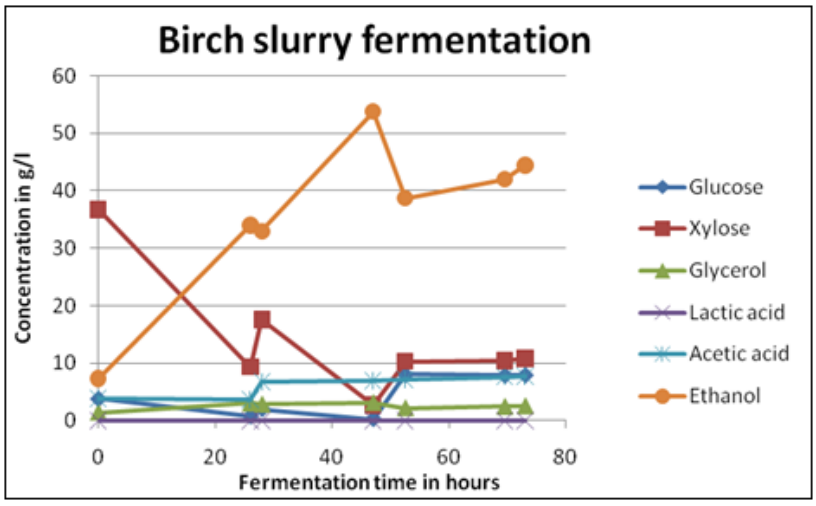

Figure 28. *Shows the HPLC-data from experiment 1. SSF on SEKAB E-Technology´s birch slurry. Y-axis display concentration given in (g/L) and x-axis display time given in hours.*

6.2.2 Discussion of Experiment 1

Experiment 1 involved a SSF with birch slurry provided by SEKAB E-Technology. Slurry was enzymatically treated with 20 mL of the enzyme Cellic Ctec2 and fermented with a pentose fermenting yeast. This experiment is considered successful since the yield of ethanol was high. Seen in retrospect, more samples should have been taken during the duration of experiment in order to achieve a curve with better precision. However, every time a sample is collected, the anaerobic conditions are disturbed, so sample extraction must always be kept at a minimum, while precision of actual concentrations must still be distinguishable.

Ethanol concentration was high once fermentation was established with values close to 40 g/L and increasing throughout the continuation of experiment. According to the three consecutive additions of slurry, the fermentation can be divided into 3 phases. In the first phase, glucose concentration decreased to 3,0 g/L, xylose concentration decreased to 27,4 g/L, whereas ethanol concentration increased to 26,6 g/L, according to the measurements. In the second phase, the glucose concentration decreased to 1,7 g/L and the xylose concentration decreased to 14,9 g/L, whereas ethanol concentration increased to 20,8 g/L. In the third phase, glucose concentration decreased to 0,06 g/L, xylose concentration increased to 0,48 g/L, ethanol concentration increased to 5,7 g/L.

In experiment 1, both xylose and glucose are utilized by pentose fermenting yeast, resulting in ethanol production. Ethanol concentration increases, as concentration of glucose and xylose decreases. The (xylose and glucose) / ethanol yield is during a short period higher than the theoretical value. Seen in figure 28 at t = 53,5 hours. Explanation for this is that there was other fermentable raw material still remaining in slurry from previous slurry additions, which is hydrolyzed during fermentation, thereby adding cumulatively to the total amount of fermentable sugars during the process. Comparing the three phases, the fermentation rate decreased during the whole process. It can be seen in data as the activity of yeast cells decreased. When the third phase was entered, cells entered a stationary stage resulting in an increase of ethanol concentration. The ethanol concentration increased moderately while (xylose and glucose) concentration levels remained stable.

6.3 Experiment 2: Washed cellulose (WC) SHF

6.3.1 Results of Experiment 2

The washed cellulose (=WC) samples from PLET, is a floccules wet matter, which contains 69,4 % water. The raw material was cellulose which had been washed three times according to PLET, and the dry mass was thus considered as 100 % pure cellulose. Three consecutive additions of WC slurry with 30,6 % dry mass content was added to the Biostat B-Plus during hydrolysis performed at 50 °C. The load of cellulose (= suspended solids) were 95,9 g/L. Temperature was decreased to 35 °C, and yeast was added at t = 72 hours at a concentration of 12,5 g/L. The total mass transferred to Biostat B-Plus was;

Cellulose: 75 g * 3 * 0,306 = 68,9 g

To simplify calculations the total volume occupied in Biostat B-Plus during the experiment was approximated as 0,75 L despite the fact that substantial volume was extracted during sampling. This effect was however counteracted by almost equal volume metric additions of NaOH-solution for pH-adjustment during both hydrolysis and fermentation. According to HPLC data the glucose concentration was 68,4 g/L.

Total volume occupied: 0,75 L
Glucose: 68,4 g/L * 0,75 L = 51,3 g
Actual hydrolysis yield = 51,3 g / 68,9 g = 0,74 g glucose / g cellulose

The fermentation yield, amount of cellulose consumed and productivity was calculated according to HPLC data, which stated that the ethanol concentration after fermentation was;

Ethanol concentration after fermentation: 30,5 g / L* 0,75 L = 22,9 g
Actual fermentation yield = 22,9 g / 51,3 g = 0,45 g ethanol / g glucose
Actual total yield = 22,9 g / 68,9 g = 0,33 g ethanol / g cellulose
Cellulose consumed = 22,9 g / (0,57 g/g * 0,9) = 44,6 g
Productivity = 22,9 g / (100 h * 0,75 L) = 0,31 g/h*L

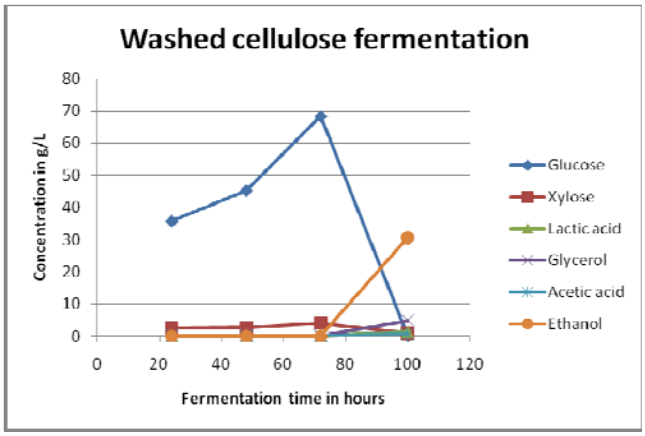

Figure 29. *HPLC data for washed cellulose. Y-axis display concentration given in (g/L) and X-axis display time given in hours.*

Table 4. *The concentration of the dry material, hydrolysis and ethanol.*

	Cellulose before hydrolysis	Glucose after hydrolysis	Ethanol after fermentation
Concentration	95,9 g/L	68,4 g/L	30,5 g/L

Table 5. *Cellulose concentration was based on dry weight measurements, glucose concentration and ethanol concentration were based on HPLC data.*

Actual hydrolysis yield	0,74 g glucose / g cellulose
Actual fermentation yield	0,45 g ethanol / g glucose
Actual total yield	0,33 g ethanol / g cellulose
Productivity (fermentation)	1,09 g/h*L
Productivity (total process)	0,31 g/h*L

6.3.2 Discussion of Experiment 2

Experiment 2 of washed cellulose is considered as a good experiment with ambiguous results since the real peak ethanol concentration cannot be determined. Still, this is a valuable result indeed, showing that the input of yeast and enzymes on pretreated biomass, can produce 0,3 tons of ethanol per ton cellulose. This yield can be converted to 99,2 US gallons per ton. It is quite high compared with USDA economically achievable yield which is in the range of 65-75 US gallons per ton [44].

However, this must also be seen in the context of how much water that was used to wash the cellulose. According to PLET the washed cellulose was washed three times with water. The productivity achieved was 1,09 g ethanol per liter per Biostat B-Plus fermentor volume and 28 hours during fermentation.

It can only be speculated that cells are starving at the end of fermentation due to difficulty to find sufficient levels of glucose as the experiment progressed. All glucose is consumed at 100 hours and ethanol concentration reached 30 g/L, which is a proof of a successful fermentation. When starving, during the last hours of fermentation the yeast cells are hence forced to consume the previously produced ethanol as an energy and carbon source in the presence of oxygen. Fully anaerobic conditions could not be performed in this experiment.

If this argumentation is correct then the obvious conclusion would be that peak ethanol concentration would be substantially above 30 g/L somewhere in the time interval between 80-90 hours. In the end, it is perhaps better to argue that there is insufficient data to say anything about peak ethanol concentration. More samples should definitely have been taken in the time interval between 72 hours to 100 hours.

6.4 Experiment 3: Unwashed cellulose SSF+SHF

6.4.1 Results of Experiment 3

Unwashed cellulose samples were extracted from a hard compact cake, which contained substantial amounts of salt. When re-suspended, the pH was 11,6, which required adjustment with H_2SO_4 to a pH of 5,5. Three batches of UWC slurry were mixed with a single addition of 25 mL Cellic Ctec2 enzyme and then hydrolyzed in the Biostat B-Plus.

Five series of hydrolyzed slurries were collected at different times to start fermentation by 10 g dry Ethanol Red yeast in shake flasks. In addition, a mixed SHF/SSF was performed with 10 g dry Ethanol Red yeast in the Biostat B-Plus in parallel with another SHF/SSF simultaneously performed in shake flask with addition of 10 g dry Ethanol Red yeast and 10 mL Cellic Ctec2 enzymes. The HPLC data and hydrolysis data are displayed in figures 30-31 and tables 6-9 show calculated yields.

In the first SHF, labeled as SHF 1 in table 6 and 7 below, the dry solid content of the unwashed cellulose sample was 88,2 %, which was re-suspended in 1,54 L. The produced glucose accumulated during the first hydrolysis was 116,4 g.

Dry raw material: 150 g * 0,882 = 132,3 g
Volume: 1,54 L
Accumulated glucose: 75,6 g/L * 1,54 L = 116,4 g
Hydrolysis yield = 116,4 g / 132,3 g = 0,88 g glucose / g dry raw material

The following 24 hour fermentation of SHF 1 in shake flasks resulted in an ethanol concentration of 41,3 g/L. The extra high yield reflects the fact that the enzyme Cellic Ctec2 still was active during fermentation. Assuming a 90 % conversion of the theoretical value for cellulose into ethanol, an estimation of how much cellulose that actually was consumed can be drawn. The fermentation yield, total yield, cellulose consumed and total productivity are calculated as follows;

Accumulated ethanol: 41,3 g/L
Fermentation yield = 41,3 g/L / 75,6 g/L = 0,55g ethanol / g dry raw material
Total yield = 0,88 g/g * 0,55 g/g = 0,48 g ethanol / g dry raw material
Cellulose consumed = (41,3 g/L * 0,1 L) / (0,57 g/g * 0,9) = 8,05 g
Productivity (fermentation) = (41,3g/L *0,1 L) / (24 h * 0,1 L) = 1,72 g/h*L
Productivity (total) = (41,3g/L *0,1 L) / (48 h * 0,1 L) = 0,86 g/h*L

The other SHF:s, SHF 1 and SHF 2 was calculated in the same way as for SHF 1, with consideration taken to the extracted volumes from Biostat B-Plus and the corresponding time. Results are presented in table 6 and 7. For the combined SSF 1 and SSF 2 fermentation, only the total yield could be calculated. Since volumes of the previous SHF:s were extracted, these must considered when calculating the actual concentration present within the Biostat B-Plus. The reached ethanol concentration is very high due to the long hydrolysis time. Data is summarized below in table 8 and 9. For the combined SSF1 performed in Biostat B-Plus; the dry raw material, volume compensation, ethanol produced, yields, cellulose consumed and productivity are calculated as follows;

Dry raw material: 365,9 g * (2,54 L - 0,15 L - 0,1 L) / 2,54 L = 329,9 g
Volume: 2,54 L - 0,15 L - 0,1 L + 0,01 L + 0,05 L = 2,35 L
Ethanol produced: 53,8 g/L * 2,35 L = 126,4 g
Total yield = 126,4 g / 329,9 g = 0,38 g ethanol / g dry raw material
Cellulose consumed = 126,4g / (0,57 g/g * 0,9) = 246,4 g
Productivity = 126,4 g / (144 h * 2,35 L) = 0,37 g/h*L

And for the combined SSF 2 performed in shake flask; the dry raw material, volume compensation, ethanol produced, yields, cellulose consumed and productivity are calculated as follows;

Dry raw material: 329,9 g * (0,1 L / 2,35 L) = 14,04 g
Volume: 0,1 L
Ethanol produced: 52,5 g/L * 0,1 L = 5,25 g
Total yield = 5,25 g / 14,04 g = 0,37 g ethanol / g dry raw material
Cellulose consumed = 5,25 g / (0,57 g/g * 0,9) = 10,23 g
Productivity = 5,25 g / (144 h * 0,1 L) = 0,36 g/h*L

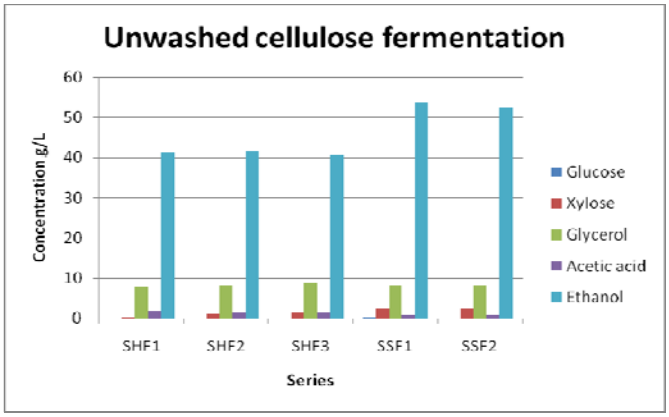

Figure 30. *HPLC-data presented in a graph for unwashed cellulose fermentation. For the SHF:s the hydrolysis continued in the Biostat B-Plus using 10 mL enzyme Cellic Ctec2, and each subsequent fermentation was performed for 24 hours, and for the combined SSF:s the time was 48 hours. In each shake flask fermentation was 1 g of Ethanol Red yeast added.*

Table 6. *Dry mass concentration during hydrolysis exceeded theoretical yield due to the fact that previously added dry material contributes cumulatively so that more sugars is produced.*

	Cellulose added before hydrolysis	Glucose after hydrolysis	Ethanol after fermentation
SHF 1	86,0 g/L	75,6 g/L	41,3 g/L
SHF 2	122,6 g/L	72,2 g/L	41,7 g/L
SHF 3	144,2 g/L	81,7 g/L	40,4 g/L

Table 7. *The SHF yield data for experiment 3.*

	SHF 1	SHF 2	SHF 3
Hydrolysis yield	0,88 g glucose / g cellulose	0,60 g glucose / g cellulose	0,57 g glucose / g cellulose
Fermentation yield	0,55 g ethanol / g glucose	0,58 g ethanol / g glucose	0,49 g ethanol / g glucose
Total yield	0,48 g ethanol / g cellulose	0,35 g ethanol / g cellulose	0,28 g ethanol / g cellulose
Productivity (fermentation)	1,72 g/h*L	1,74 g/h*L	1,68 g/h*L
Productivity (total)	0,86 g/h*L	0,58 g/h*L	0,28 g/h*L

Table 8. *The combined SSF 1and SSF 2, concentration and yield data for experiment 3.*

	Combined SSF 1	Combined SSF 2
Cellulose added before SSF	144,2 g/L	144,2 g/L
Final ethanol concentration	53,8 g/L	52,5 g/L
Actual total yield	0,38 g ethanol / g cellulose	0,37 g ethanol / g cellulose
Productivity	0,37 g/h*L	0,36 g/h*L

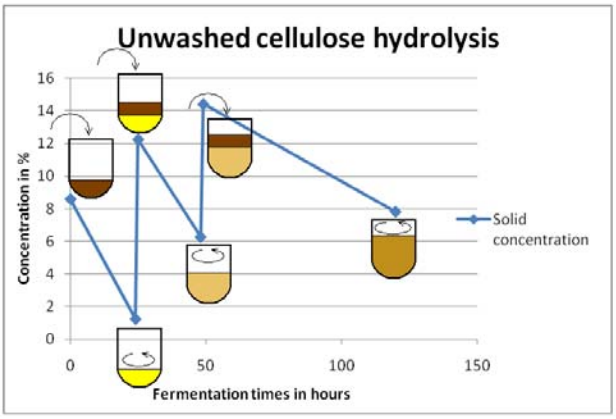

Figure 31. *Hydrolysis curve of unwashed cellulose. After each slurry addition, the solid concentration increases due to the extra addition of solids, then it decreases due to ongoing hydrolysis.*

6.4.2 Discussion of Experiment 3

The decreasing hydrolysis rate during experiment can be explained with a decrease of the enzymatic activity. The SSF 1 and SSF 2 both had higher total yield than SHF 3, since an extra addition of 10 mL Cellic Ctec2 enzymes were added to the Biostat B-Plus, when these were initiated. In addition, the combined SSF1 and SSF2 both had access to hydrolyzed material not yet converted by the enzyme Cellic Ctec2. In laboratory experiments, enzyme cost are often neglected, but in industrial production, the cost of enzymes must be considered. Higher yield versus lower cost is always important to consider if the laboratory experiments ever will find an industrial platform.

The most interesting results are found in the SHF, where the actual ethanol yield range between 0,48 - 0,28 g ethanol / g cellulose. This provides a strong argument for a future production of lignocellulosic ethanol from unwashed cellulose from the simple pre-treatment developed by PLET. The higher yields (0,37 - 0,38 g ethanol / g cellulose) accumulated in the combined SSF:s are also inspiring, but are somewhat inconclusive since it is hard to rule out the cumulative effect of the ongoing hydrolysis.

Experiment 3 has undoubtedly provided this master thesis with the best experimental results. It is, however, also the hardest one to interpret since it was a combined SSF and SHF experiment. The ethanol yield was very high, close to the theoretical yield. It is preferable to use unwashed cellulose in industrial ethanol production to reduce the use of water, which eventually will have to be removed in distillation at great cost.

The Biostat B-Plus was used as a separate hydrolysis reactor from which batches were taken every day to start fermentation in shake flasks. Only one end sample was taken from the fermentations in shake flasks to prove the production of ethanol. More samples should have been collected during experimentation. As everything turned out, there was still substantial ethanol content in all shake flasks, thereby proving that pre-treated unwashed cellulose from PLET is excellent for making industrial ethanol. For the combined SSF:s results, the Biostat B-Plus was used as a standard SSF bioreactor loaded with enzymes in large excess to see if complete conversion of cellulose into glucose could generate a much higher ethanol yield compared to the previous separate fermentation performed in shake flasks. The main reason for this approach is to see if the increased ethanol yield could compensate the extra use of enzymes.

6.5 Experiment 4: Sweet liquor (10 flasks)

6.5.1 Results of Experiment 4

The HPLC-data indicate no sign of successful fermentation in experiment 4. Five sets of media were prepared from sweet liquor and autoclaved water at different dilutions. All series of media were mixed with an additional nitrogen source and pentose fermenting yeast as fermenting organism. The initial sugar concentration was however not determined.

Table 9. *HPLC data of experiment 4.*

Samples	10:40 ml	20:30 ml	30:20 ml	40:10 ml	50:0 ml
Xylose (g/L)	1,79	2,40	3,24	3,89	3,76
Lactic acid (g/L)	0	0	0	2,24	3,16
Glycerol (g/L)	0	0	0	0,29	0,30
Acetic acid (g/L)	0,29	0,81	0,91	0,71	0.68
Ethanol (g/L)	3,60	1,85	3,35	3.40	3,18

6.5.2 Discussion of Experiment 4

Experiment 4 from PLET samples is considered as a failed experiment since the sweet liquor did not contain sufficient fermentable sugars, which made fermentation unfeasible. The initial sugar concentration was not determined. HPLC data shows only the presence of contaminations and a large percentage of smaller hydrocarbons. The low concentration of ethanol is most probably coming from the transferred pre-cultured yeast cell medium, thus would have nothing to do with fermentation of sweet liquor.

6.6 Experiment 5: Sweet liquor (9 bottles)

6.6.1 Result of Experiment 5

A medium was prepared from sweet liquor and autoclaved water. This medium was separated into 9 bottles and yeast extract and different amounts of yeast cells were added. Samples were extracted and analyzed after 72 hours of fermentation. No sign of successful fermentation according to HPLC data.

Table 10. *HPLC data of experiment 5. Where A, B and C refers to the initial cell concentration respectively concentration 0,5 g/L, 1,0 g/L and 1,5 g/L. The numbers 1,4 and 7 refer to bottle with no yeast extract added while 2,5 and 8 refer to addition of 1,0 g/L of yeast extract and finally 3, 6 and 9 are bottles with 5,0 g/L addition of yeast extract.*

Samples	A1	A2	A3	B4	B5	B6	C7	C8	C9
Lactic acid (g/L)	3,66	4,03	3,89	3,82	3,70	3,81	3,65	3,77	3,78
Acetic acid (g/L)	0,57	0,75	0,62	0,52	0,51	0,58	0,46	0,49	0,50

6.6.2 Discussion of Experiment 5

Experiment 5 from PLET samples is considered as a more or less failed experiment since the sweet liquor did not contain sufficient fermentable sugars, which made fermentation unfeasible. HPLC data shows only the presence of contaminations and a large percentage of small hydrocarbons.

6.7 Experiment 6: Lignin (Dry weight / Polycondensation)

6.7.1 Results of Experiment 6

A polycondensation experiment was performed by complete mixing of 10 g lignin with 0,2 g $NaOH_{(s)}$ and 10 g furfural $(OC_4H_3CHO)_{(l)}$. The mixture was then incubated at 150 °C for 20 minutes, after which it was cooled to 20°C. The polycondensation was complemented with dry weight estimation. The pure lignin from PLET has a dry solid percentage of 63,8 %. When subjected to a polycondensation the result was a hydrophobically insoluble, brittle, porous, tarnish black cake.

6.7.2 Discussion of Experiment 6

The pure lignin of PLET looks like small brownish granules. These granules are hydrophilic and have rosin like melting and freezing behavior, mostly amorphous. Phenol formaldehyde resins (PF) include synthetic thermosetting resins such as obtained by the reaction of phenols with formaldehyde and similar chemicals such as furfural. Lignin monomers have phenolic hydroxyl group. Lignin can be used as a phenol in polycondensation reaction.

Experiment 6 was only a short study of general properties. Since this master thesis did not get access to necessary analyzing equipment it was impossible to conduct any scientific analysis better than analysis already performed by PLET. It is however a bit disturbing that the product of the polycondensation was so brittle. That is, if the pure lignin ever will be applied as a binder or adhesive in paint of glues. Heating as well as pressure applied in experiment was substantially lower than what is normally applied in industry for adhesives production. Probably the preferred adhesive characteristics will be achieved under those conditions.

7. Conclusions.

7.1 Conclusions of results discussed in general

Best ethanol yield was obtained in the experiments with the raw material of unwashed cellulose, followed by less yield of accumulated ethanol from washed cellulose samples and birch slurry samples.

The stickiness of slurry can be a certain problem in experiments. High solid concentration slurry was hard to stir, as the result, faster stirring speed and extra addition of water must be used on slurries before hydrolysis.

In experiment 1, the ethanol yield from dry material obtained for hardwood birch slurry was 0,23 g ethanol / g dry raw material. Whereas in experiment 2, the ethanol yield from dry material obtained for softwood pine washed cellulose was 0,32 g ethanol / g cellulose. And in experiment 3, the ethanol yield from dry material obtained for softwood pine unwashed cellulose in the three SHF was; 0,48, 0,34 and 0,28 (g ethanol / g cellulose) respectively, while the yield was 0,37 and 0,38 g ethanol / g cellulose in the two combined SSF:s. It is interesting that the unwashed cellulose in experiment 3 achieve a slightly higher ethanol concentration compared to the washed cellulose in experiment 2.

Main reason for the increased ethanol yield in experiment 3 compared to experiment 2, is a more complete hydrolysis due to higher enzymatic loading, and that the enzyme Cellic Ctec2 perform better on not absolutely pure cellulose [10]. Decrease of ethanol yield during the three SHF:s in experiment 3 are most probably caused by diminished enzymatic activity, due to product inhibition (glucose concentration is high) and increasing inaccessibility of the substrate in a larger volume.

The fermentation strains, Ethanol Red and the pentose fermenting yeast are both especially developed for the purpose of ethanol production. However, the pentose phosphate pathway is not relevant in the metabolism of Ethanol red strains, thus the pentoses present are only occupying space as not fermentable sugars, whereas in pentose fermenting yeast these pentoses are contributing to increase ethanol yield. This effect is reduced by the fact that softwood only contains a smaller percentage of hemi-cellulose, while a fermenting strain utilizing pentose phosphate pathway is absolutely necessary when using hardwood birch as a substrate. When comparing the accumulated ethanol yield from either fermenting organism, this is important to consider.

There is, however, some general differences that need to be considered between the samples of the two companies, SEKAB E-Technology and PLET. Evidently, SEKAB E-Technology has had time to optimize process parameters of their pre-treatment over several years with a lot of manpower, money and advanced equipment, while PLET have had to make the best of what they have had at their disposal. In addition, there are a lot of other companies that uses dilute SO_2 as a pre-treatment, while no other currently known company uses dilute nitric acid as pre-treatment of lignocellulosic material, at least not in the way PLET does it. In this context SEKAB E-technology is clearly favoured.

Birch slurry of SEKAB E-Technology is of hardwood origin, while the Gorman pine samples of PLET comes from cellulose rich softwood. The hardwood birch slurry contains more inhibitors regarding fermentation compared to the softwood pine. In addition, the washed

cellulose samples from PLET are referred to as pure cellulose, which substantially increases the potential ethanol yield, if put into a SSF and/or SHF. Thus have hemi-cellulose dominated hardwoods both benefits and backdraughts for industrial potential, compared to cellulose dominating softwoods.

Furthermore, fermenting organisms applied in SSF:s on pre-treated samples are different, pentose fermenting yeast for hemi-cellulose rich samples (pentose sugars generating) from SEKAB E-Technology, and Ethanol Red which was applied on cellulose rich (hexose sugars generating) samples from PLET. Hexoses are clearly favoured compared to pentoses, since they are more easily metabolized by already established and preferred metabolic pathways in yeast. The metabolic pentose phosphate pathway is generally not expressed under normal fermentation conditions, whereas the glucose pathway is utilized by yeast as long as there is any glucose still present in media, which further delays the metabolic fermentation of pentoses into ethanol.

Purpose of pre-treatment is to break up the lignocellulosic matrix. The approach is to separate all three major components; cellulose, hemi-cellulose and lignin. It is apparent that the yield of fermentable sugars would be greater if a larger proportion of separated cellulose fraction can be recovered after a successful pre-treatment. Although, SEKAB E-Technology and PLET both use dilute acids in pre-treatment to avoid unnecessary fractional loss of desirable products, the process of PLET must be considered favoured because of milder process conditions, (= lower temperature and low pressure).

The question is, if the pre-treatment performed by PLET really break up the lignocellulosic matrix to a sufficient degree, without producing unwanted inhibitors like furfurals, HMF (= 5-Hydroxymethylfurfural), levulinic acid (= 4-oxopentanoic acid), and excessive loss of the expected products. The answer is that ethanol could be produced at high yield and low cost from the pre-treated cellulose fraction, when enzymes such as Cellic Ctec2 and microorganisms such as Ethanol Red are incorporated in the process.

Moreover, the enzymatic treatment with Cellic Ctec2 efficiency could also vary between the two pre-treatment technologies, since residues of either sulphur or nitrates or other inhibitors could interfere and decrease enzymatic activity, but this is just speculation. More experiments need to be performed to fully evaluate minimum enzyme loading contra substrate loading, to optimize the whole process if the concept will ever see an industrial application.

The Biostat B-Plus fermentor used in SSF and SHF experiments does not fully provide anaerobic conditions, which further decreases the yield of ethanol when yeast metabolize previously produced ethanol during the latter phase of fermentation. Samples extracted were frozen and thawed one time too much before analyzed in HPLC, due to rescheduled planning, which also could have generated minor losses of evaporated ethanol.

As has been shown by the so called “failed” experiments 4 and 5, on sweet liquor from PLET it is clear that this fraction probably contain the majority of all other constituents found in wood, including inhibitors such as HMF (= 5-Hydroxymethylfurfural), Levulinic acid (= 4-oxopentanoic acid) and salts. It would be interesting to apply Torula yeast, as suggested by PLET, on this fraction to see if a commercial grade unicellular protein actually can be produced instead.

7.2 Conclusions on the commercial potential

Before doing anything, the commercial potential of the concept have to be thoroughly evaluated and specified in a time schedule. Activities such as networking, mutual partnership agreements, licence agreements, patent rights, complementary research and process optimization, logistics, funding and production plant design, according to appropriate specifications must be organized within the project in order to ensure success.

At least 40 million SEK is needed as a minimum starting capital to be able to construct a small commercially viable pilot plant, according to PLET [26]. This investment would cover the basic requirements and is scalable. The construction could preferably be done in Sweden in the vicinity of an existing saw mill or paper pulp industry or elsewhere, where a steady supply of cheap raw material could be assured. Size of the operation envisioned, depends greatly on location and adjacent businesses. Large pulp mills in the range of 400-500 MWh would be preferred, the largest pulp mills in Canada process 5000 ton per day which is equivalent to a capacity of 1 GW wood per day (GW = giga watt) [45], but the concept of the technology of PLET must first prove its value in a much smaller scale. An initial investment of about 30 - 40 million SEK is thus reasonable in the first phase, and could later on be scaled up by adding multiple production lines [26].

Despite the simple design of CRP compared to conventional technology, it is hard to explain to investors and venture capitalist the whole concept. This is a general problem for the concept of bio-refining as a whole and not just for the concept of PLET, compared to the already established oil refinery industry, where practically all by-products generated by its refining processes have already found appropriate commercialization.

According to PLET there are some problems related to unwanted nitration on the aromatic ring of the main product Pure Lignin. This could actually be an advantage, given the possibility that a future not yet known application would be found. Nitration on aromatic rings are for example found in explosives such as trinitrotoluen (=TNT) [46]. Perhaps there is a commercial potential to produce new explosives from the pure lignin of PLET as well, or just to use the pure lignin as a raw material for TNT-production.

Unfortunately, because of the nitration of the lignin, it would not be recommended to use it as a combustible fuel, due to environmental regulations regarding emissions of nitrous gases. This is a major problem, considering that the lignin is regarded as a source of energy when incinerated in a heat and power plant. And this means that some commercial use of the lignin must be found. One such possibility is to use it as an additive in paint and other adhesive applications, where the pure lignin would perform well, thanks to its water solubility and high molecular weight.

Currently, it is extremely hard to find investors in Sweden because of general financial instability on the global markets. Especially while networking it was experienced that the patent issues were extremely important since the technology is not of Swedish origin. Very few Swedish investors appreciate and recognize an already approved patent as an attractive investment possibility unless it is domestic. A world patent such as the one PLET possesses would cost several hundred thousand SEK according to the Swedish PRV (= Patent och registreringsverket) [47], and it took PLET several years of processing before it was approved. Despite promises of an agreement to utilize a patented technology under licence, it is really hard to attract the interest from venture capitalist and other agencies.

The promise of a substantial capital investment inserted into the business is not a powerful argument for co-investors either. A small business such as PLET has not the sufficient support of a large organization. Neither does a small consulting business such as the one envisioned here in Sweden. It is important to understand that the initial investment must come from many different sources. Required funding, must be granted by multiple sources, such as national and international research programmes, scholarships, bank loans, own capital, venture capitalist, business institutes, crowd funding initiatives et c.

But more importantly, there is an urgent need for connections and business network, in order to find the appropriate representatives who have the business expertise and know how to set up business arrangements. It is evident that a "snowball effect" will spring into action once a major investor is found, but that is far from an eventual completion of a project.

It is by far too soon to discard the simple, environmentally friendly low cost pre-treatment method of PLET as a plausible alternative to produce next generation of lignocellulosic ethanol. More studies on samples derived from the pilot plant in Canada must be done as soon as possible. Positive results from these future studies would eventually lead to the construction of a larger demonstration plant, which would be used for even further analysis and optimization of process parameters.

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From: Sandra Brinckerhoff

Subject: clean and renewable options

Make oil from algae.

From: Burt Brinckerhoff
Subject: clean and renewable energy

Protect our most precious natural resource - our children and grandchildren. Make oil from algae.

Burt Brinckerhoff

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Subject: The government wants your advices on biofuels

Letter 1: General suggestions on biofuels decision making
Letter 2: Out-of-the-box solution for the bio-economy

To Whom It May Concern,

I really appreciate this opportunity to express my opinions on biofuels. I did it several times by publishing papers in scientific journals and am happy to send my opinions to the right administrative. As a new USA citizen, I would like to do my best to help the USA establish the reviving bioeconomy and regain No. 1 manufacturing nation position in the world. In Letter One, I will introduce myself and provide some suggestions about biofuels policy making. In Letter Two, I will present an out-of-the-box solution to the bioeconomy and how to re-shape the future bioeconomy.

First, let me introduce myself. I am an associate professor with tenure of Biological Systems Engineering Department of Virginia Tech. (With protection of tenure, I dare to speak my opinion openly.) I have received my degrees of Biochemical Engineering Bachelor and Master (China) and Ph.D. (Dartmouth College, USA). I have worked on biofuels since 1997, under supervision of biofuels pioneers Profs Lee Lynd and Charles Wyman. I think that I am qualified for making some comments and suggestions due to numerous reasons: (1) long-time training and studies in this field, (2) the broadest research topics in biofuels field as a single PI in the USA from pretreatment, cellulase engineering, consolidated bioprocessing bug development, metabolic engineering, synthetic biology, water conservation, food and feed production, and energy efficiency analysis, (3) different education and cultural backgrounds so that I can find out some blind spots, which most persons are ignoring, (4) a good record in biofuels R&D based on publications, grants, citations, and awards, (5) a brave and insightful thinker, who dare stand out to criticize non-sense biofuels R&D projects openly, and (6) an amateur historian, especially in science and technology. To partially support my claims: I am listing several of my achievements in R&D and their commercialization:

(1) Discovering a new metabolic pathway for *Clostridium thermocellum* and validated technological feasibility of consolidated bioprocessing (CBP) concept. As a result, the DOE biomass program accepted it as an ultra-low production platform for cellulosic ethanol in 2006. Now the DOE Bioenergy Science Center and Mascoma are working on this direction. Mascoma will go to IPO by the end of this year. This work was mainly done by me, along with my Ph.D. advisor Lee Lynd.

(2) Invented a cellulose-solvent and organic solvent-based lignocellulose fractionation (COSLIF), when I was an assistant professor at Virginia Tech. Now this technology has been licensed to Optafuel Co, which has a 25 MM investment for building a pilot plant in South Virginia.
(3) Founded a biofuels start-up company – Gate Fuels Inc. It is funded by NSF SBIR I and BioMethodes Co.
(4) Achieved the most energy efficiency way for the generation of hydrogen from renewable sugars. I am a receipt of Air Force Young Investigator Award (2008). Now Shell GameChange program is funding our efforts in commercializing this process (Note: *This technology is the most important technological breakthrough in the future bioeconomy. Please see my second letter. Its importance at least equals that of ammonia synthesis*).
(5) Accomplished low-cost conversion of non-food cellulose to edible starch. This technology is under negotiation with a Chinese animal feed producer. We would solve the problem of feeding the world.

Second, history always teaches us a lot and it repeats itself in different forms. Recalling the successful story of making atomic bombs in the USA and China. The USA case tells us that **we need good leaders** (e.g., J Robert Oppenheim), who are quick to learn new things, are good communicators, are open to different opinions, dare to make decisions, do not think too much of his personal interests, and believe that national interests are beyond personal interests. Based on my observation, most USA biofuels leaders do not have such quality. Some famous biofuels scientists are leading the USA to wrong directions due to their personal interests (job security, money, and fame). As a result, it could kill the bright future of biofuels. The Chinese case tells us that (1) big democracy in science and technology is a must to avoid possible wrong directions (i.e., everyone has a chance to doubt or criticize research plan openly) and (2) concentration of limited money for to the best and well-analyzed projects and then achieving the goals within the shortest time. My suggestion is open debate and open discussion (it is not enough to do it in scientific journals). In this new system, any persons regardless of his ranking, university, and education background have a chance to raise his doubts or challenge established or leading scientists; such leading scientists must have their responsibilities to address such doubts openly. We need several round open debates until the doubts have been addressed clearly and openly. We may introduce open scientific and technological competitions like American Idol. ***We need big democracy in S&T. We need dual-way evaluation and feedback rather than one-way judgment. Successful scientists in their fields do not mean that they are experts in another field.*** (Note: there are so many instant biofuels experts. In reality, they know little.)

Third, we need biofuels leaders with great visions plus doable technology plans. Only vision cannot solve practical energy problems. Otherwise, science fiction writers might be best leaders. In reality, so many energy leaders are doing things like science fiction writers do. They may have right visions but they do not know how to do it. Day dream plans will waste tax-payer money and results in wrong decisions. My vision is to replace crude oil with renewable sugar when we can increase biomass energy utilization efficiency. Also, we have provide very detailed technical solutions as shown in the below papers.

- Zhang Y-HP, Mielenz JR. 2011. Renewable hydrogen carrier -- carbohydrate: constructing the carbon-neutral carbohydrate economy. Energies 4:254-275.

- Zhang Y-HP. 2009. A sweet out-of-the-box solution to the hydrogen economy: is the sugar-powered car science fiction? Energy Environ. Sci. 2(2):272-282.
- Zhang Y-HP. 2011. Simpler is better: high-yield and potential low-cost biofuels production through cell-free synthetic pathway biotransformation (SyPaB). ACS Catal. 1:998-1009.

According to our analysis, the USA has enough biomass resource to replace all oil used in the transportation sector.

- Huang WD, Zhang Y-HP. 2011. Energy efficiency analysis: biomass-to-wheel efficiency related with biofuels production, fuel distribution, and powertrain systems. PLoS One 6(7):e22113.

To my knowledge, Germany and Chinese Governments are supporting this new direction, opened by me. **My worry is that the USA invention does not mean the USA innovation, if we do not take action now.**

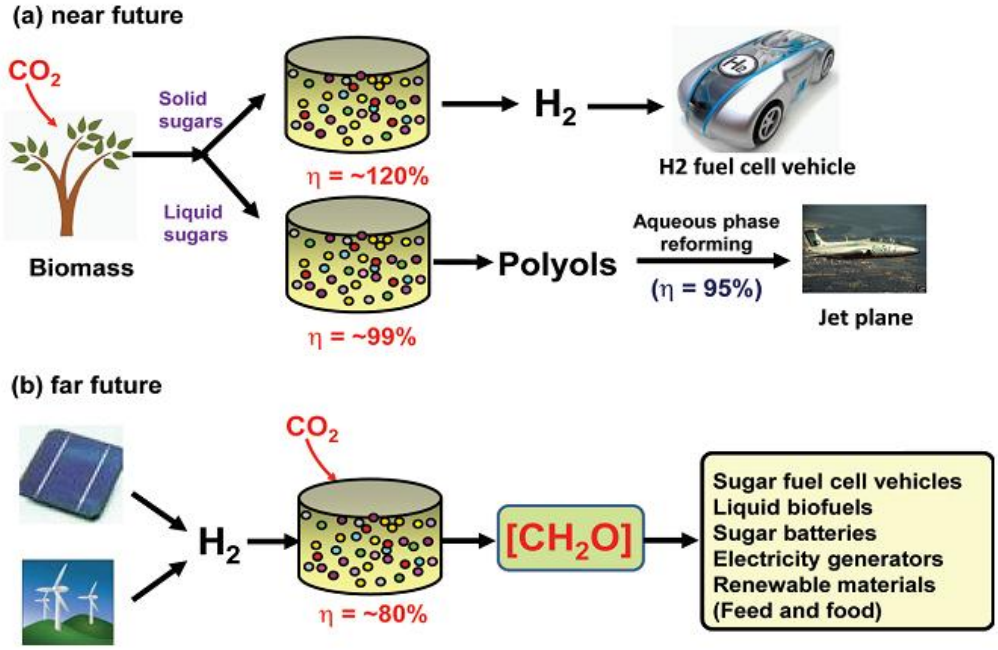

Figure 1. Different biofuels scenarios based on plant biomass through natural photosynthesis (near future) and starch produced by artificial photosynthesis (far future).

Fourth, we must search for the clarity of the bioeconomy R&D. *Not every possibility is worth testing.* Like Tobacco company's doing (studies that tobacco may not be bad to health in 1960-1970s), some oil companies (e.g., Exxon Mobile) are misleading biofuels directions on purpose. We need refocus on our biofuels directions. I summarize several key points:

1. Economic goals of biofuel R&D projects must be finished within a defined timeframe with numerous clear and hidden constraints plus political and geographic concerns;
2. Thermodynamics (energy conversion efficiency based on mass balance and energy balance) determines economics in the long term;

3. Energy efficiency analysis is simpler and more transparent than life cycle analysis and process economic analysis;
4. R&D can drastically decrease production costs but cannot break the limits set by thermodynamics, energetics, and physical and chemical properties of materials;
5. Not every biofuels possibility deserves more research. Muddy water strategy would delay biofuels' wide implementation or even kill biofuels' future;
6. Moore's law does not work in the energy field for bother energy efficiencies and production costs due to the above-mentioned limits; and
7. Renewable energy sources could eventually replace most non-renewable fossil fuel sources, but this transition would take at least a half century.

Fifth, do not fund any big biofuels projects. The DOE Bioenergy Centers and USDA CAP projects cannot work. Funding big biofuels project must have a condition that these projects must pass through thorough open debates and examination.

Sixth, capping federal grants to any single researcher, e.g., one million dollars per year. We need encourage competition. Most times top scientists do not guide postdocs or students because they do not know technical details. Fundamental researchers cannot spend too much tax-payer money. For applied research, scientists should raise their grants or funding from private sources.

I appreciate your interests and reading. If you have any question, please feel free to contact me via email at biofuels@vt.edu, or by telephone, at 01-540-231-7414.

Yours sincerely

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Subject: The government wants your advices on biofuels

Letter 1: General suggestions on biofuels decision making
Letter 2: Out-of-the-box solutions for the bio-economy

To Whom It May Concern,

In response to the open call from OSTP, this letter is my second letter. In Letter One, I introduce myself and provide some opinions about decision making for biofuels and bioeconomy. In Letter Two, I would like to share our vision and provide technical solutions.

The USA has been entering a technological plateau since 1980s. As a result, the USA is losing its ability for creating a large number of high-pay manufacturing jobs. The bioeconomy will be a savior for creating numerous jobs that cannot be outsourced. The Office of Science and Technology Policy makes a right decision for the future of USA but how to achieve it is another key question.

We need a paradigm shift. Since the USA had picked up all low-hanging (technological) fruits, only a new paradigm shift will allow us to discover a new world. Synthetic biology is receiving wide attention. But classic (in vivo) synthetic biology is not a game changer in the bioeconomy. The reason is its low production efficiency relying on living microorganisms. In fact, living entities keep duplicating themselves rather than producing the desired products only. For thousands of years, we are used to using living microorganisms for fermentation, e.g., beer, cheese, wine, ethanol, etc. In fact, living biocatalysts is not necessary. Most persons cannot think outside the box due to their habit of reasoning. We propose the use of cascade enzyme biocatalysis replacing traditional fermentations. Several important reactions have been accomplished by this new system, while they cannot be done by micro-organisms, for example, a low-cost and high-efficiency conversion of cellulose to starch, the production of 12 mol of hydrogen from one mol of glucose. The latter example is highlighted by the Royal Society of the UK as a good example of synthetic biology in 2007.

We envision a future carbon-neutral carbohydrate economy (below figure). Both natural and this newly-designed artificial photosynthesis are responsible for fixing CO_2 by utilizing solar energy; while the degradation of carbohydrate and its derivatives will release CO_2 to the atmosphere. Carbohydrate, which is renewable, carbon-neutral, and evenly distributed, will replace oil because of lower costs ($/GJ), better performance in

the transport sector, better safety, and more applications (e.g., hydrogen carrier and electricity storage compound).

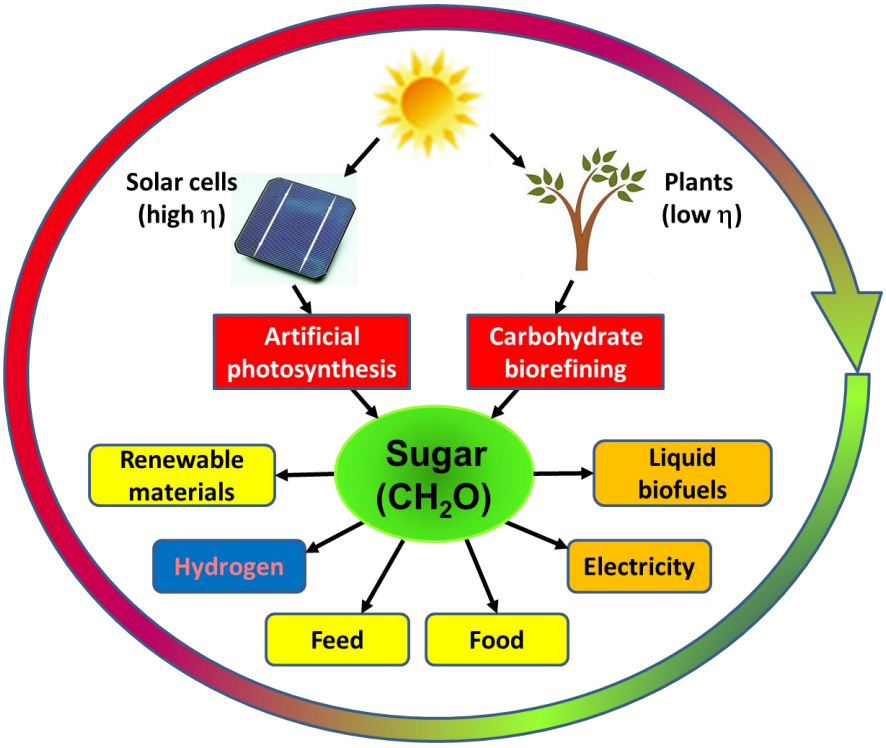

Figure. The carbon-neutral cycle based on carbohydrates as food, feed, a source of renewable material precursors (e.g., lactic acid, isoprene, succinic acid), an electricity storage carrier (e.g., ~10-14 MJ electricity output/kg), and a hydrogen carrier with a hydrogen storage capacity of 8.33-14.8 H_2 mass%.

In this package, please find five papers representing our key points:
Paper 1 (PONE 2007) – a seminal paper – sweet hydrogen generation from sugar. It is highlighted by the Royal Society of UK, ACS, and ASM. It is very terrible for most US funding agencies not to fund it because it is outside the box. (We submitted 10 DOE proposals and 5 NSF proposals. All were rejected). *Now German and Chinese governments are funding similar R&D efforts.* If the USA does not take action now, the USA might lose race in renewable energy because Germany is stronger than USA in the industrial enzyme field. Since Germany scientists knows right directions proposed by me, they could utilize their advantage and achieve the bioeconomy before the USA. As a result, *the USA invention does not equal the USA innovation*.

Paper 2 (EES sugar car 2009). We clearly explain why this technology is an out-of-the box solution to the hydrogen economy and bioeconomy. This vision is against interests of most H2 R&D persons.

Paper 3 (carbohydrate is H2 carrier, 2010). The use of biomass sugars as a high density hydrogen carrier, better than methanol and others. *This is against general interests of hydrogen storage persons.*

Paper 4 (PONE fuel independence 2011). Our analysis clearly suggests that it is possible to replace all gasoline by using a small fraction of biomass resource if we can increase biomass utilization efficiency. Clearly, our solution can be scaled up easily than other solutions. *This is against general interests of most biofuels experts.*

Paper 5 (ACS Cat. Simpler 2011). This perspective clearly explains that our technology SyPaB is an incremental technology, but its impact will be revolutionary. The implementation of this technology is doable based on ready knowledge and technology. Its impacts would impact a lot of fields, such as biomass, hydrogen, fuel cells, batteries, CO_2 fixation, water, agriculture, and vehicles.

I appreciate your interests and reading. If you have any question, please feel free to contact me via email at biofuels@vt.edu, or by telephone, at 01-540-231-7414.

Yours sincerely

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PLoS one

High-Yield Hydrogen Production from Starch and Water by a Synthetic Enzymatic Pathway

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Background. **The future hydrogen economy offers a compelling energy vision, but there are four main obstacles: hydrogen production, storage, and distribution, as well as fuel cells. Hydrogen production from inexpensive abundant renewable biomass can produce cheaper hydrogen, decrease reliance on fossil fuels, and achieve zero net greenhouse gas emissions, but current chemical and biological means suffer from low hydrogen yields and/or severe reaction conditions.** ***Methodology/Principal Findings.*** **Here we demonstrate a synthetic enzymatic pathway consisting of 13 enzymes for producing hydrogen from starch and water. The stoichiometric reaction is $C_6H_{10}O_5$ (l)+7 H_2O (l)→12 H_2 (g)+6 CO_2 (g). The overall process is spontaneous and unidirectional because of a negative Gibbs free energy and separation of the gaseous products with the aqueous reactants.** ***Conclusions.*** **Enzymatic hydrogen production from starch and water mediated by 13 enzymes occurred at 30°C as expected, and the hydrogen yields were much higher than the theoretical limit (4 H_2/glucose) of anaerobic fermentations.** ***Significance.*** **The unique features, such as mild reaction conditions (30°C and atmospheric pressure), high hydrogen yields, likely low production costs ($\sim$2/kg H_2), and a high energy-density carrier starch (14.8 H_2-based mass%), provide great potential for mobile applications. With technology improvements and integration with fuel cells, this technology also solves the challenges associated with hydrogen storage, distribution, and infrastructure in the hydrogen economy.**

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INTRODUCTION

Photosynthesis is the biological process that converts light energy to chemical energy and stores it in carbohydrates as "6 CO_2 + 6 H_2O→$C_6H_{12}O_6$+6 O_2", and fixes atmospheric carbon into biomass (living carbon). Before the industrial revolution, the global economy was largely based on carbon extracted directly or indirectly (via animals) from plants; now the economy is mainly dependent on fossil fuels (dead carbon). At the dawn of the 21st century, a combination of economic, technological, resource, and political developments is driving the emergence of a new carbohydrate economy [1,2].

Climate change, mainly due to CO_2 emissions from fossil fuel burning, and the eventual depletion of the world's fossil-fuel reserves, are threatening sustainable development [2–4]. Abundant, clean, and carbon-neutral hydrogen is widely believed to be the ultimate mobile energy carrier replacing gasoline, diesel, and ethanol; a high energy conversion efficiency ($\sim$50–70%) can be achieved *via* fuel cells without producing pollutants [3]. Four main R&D priorities for the future hydrogen economy are: 1) decreasing hydrogen production costs *via* a number of means, 2) finding viable methods for high-density hydrogen storage, 3) establishing a safe and effective infrastructure for seamless delivery of hydrogen from production to storage to use, and 4) dramatically lowering the costs of fuel cells and improving their durability [5–7]. Hydrogen production from less costly abundant biomass is a shortcut for producing low-cost hydrogen without net carbon emissions [8–15].

Synthetic biology is interpreted as the engineering-driven building of increasingly complex biological entities for novel applications, involving the steps of standardization, decoupling, abstraction, and evolution [16]. One main goal of synthetic biology is to assemble interchangeable parts from natural biology into the systems that function unnaturally [17]. The simplest synthetic biology example is to assemble enzymes to implement an unnatural process, in which the gene regulatory systems do not exist. Here we apply the principles of synthetic biology to implement an important reaction by using 13 well-known enzymes, which form an unnatural enzymatic pathway. The most obvious advantage of this process is that the hydrogen yield is far higher than the theoretical yield (4 H_2/glucose) of biological hydrogen fermentations [9,15,18]. This novel enzymatic high-yield hydrogen production method is anticipated to have great impacts on the future hydrogen and carbohydrate economy.

RESULTS

We designed a new enzymatic method for producing hydrogen from starch and water,

$$C_6H_{10}O_5\ (l) + 7\ H_2O\ (l) \rightarrow 12\ H_2\ (g) + 6\ CO_2\ (g) \qquad (1)$$

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Competing Interests: YHPZ and JRM are the co-inventors of this enzymatic hydrogen production process, which is covered under provisional patent application.

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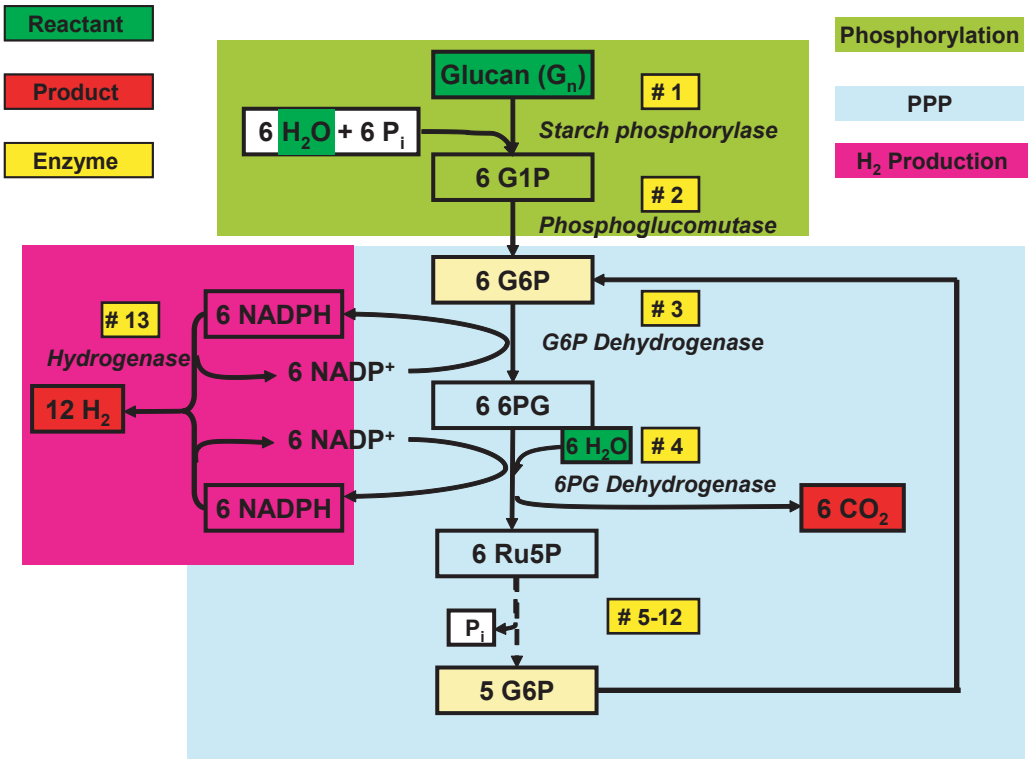

Figure 1. The synthetic metabolic pathway for conversion of polysaccharides and water to hydrogen and carbon dioxide. The abbreviations are: PPP, pentose phosphate pathway; G1P, glucose-1-phosphate; G6P, glucose-6-phosphate; 6PG, 6-phosphogluconate; Ru5P, ribulose-5-phosphate; and P_i, inorganic phosphate. The enzymes are: #1, glucan phosphorylase; #2, phosphoglucomutase; #3, G-6-P dehydrogenase; #4, 6-phosphogluconate dehydrogenase, #5 Phosphoribose isomerase; #6, Ribulose 5-phosphate epimerase; #7, Transaldolase; #8, Transketolase, #9, Triose phosphate isomerase; #10, Aldolase, #11, Phosphoglucose isomerase: #12, Fructose-1, 6-bisphosphatase; and #13, Hydrogenase.
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Figure 1 shows the synthetic enzymatic pathway that does not exist in nature. It is comprised of 13 reversible enzymatic reactions: a) a chain-shortening phosphorylation reaction catalyzed by starch phosphorylase yielding glucose-1-phosphate (Equation 2) [19]; b) the conversion of glucose-1-phosphate (G-1-P) to glucose-6-phosphate (G-6-P) catalyzed by phosphoglucomutase (Equation 3) [20]; c) a pentose phosphate pathway containing 10 enzymes (Equation 4) [21]; and d) hydrogen generation from NADPH catalyzed by hydrogenase (Equation 5) [22].

$$(C_6H_{10}O_5)_n + H_2O + P_i \leftrightarrow (C_6H_{10}O_5)_{n-1} + G-1-P \quad (2)$$

$$G-1-P \leftrightarrow G-6-P \quad (3)$$

$$G-6-P + 12\ NADP^+ + 6\ H_2O \leftrightarrow 12\ NADPH + 12\ H^+ + 6\ CO_2 + P_i \quad (4)$$

$$12\ NADPH + 12\ H^+ \leftrightarrow 12\ H_2 + 12\ NADP^+ \quad (5)$$

We first validated the reaction scheme of Woodward et al. [23], in which hydrogen was produced from G-6-P via 11 enzymes, based on the reaction of G-6-P+6 $H_2O \rightarrow 12\ H_2+6\ CO_2+P_i$ (top curve in Fig. 2). The proof-of-principle experiment was then conducted to validate whether hydrogen can be produced from starch and water at 30°C using 13 enzymes (see Materials and Methods). Clearly, hydrogen was produced as expected (bottom curve in Fig. 2). As compared to using G-6-P as the substrate,

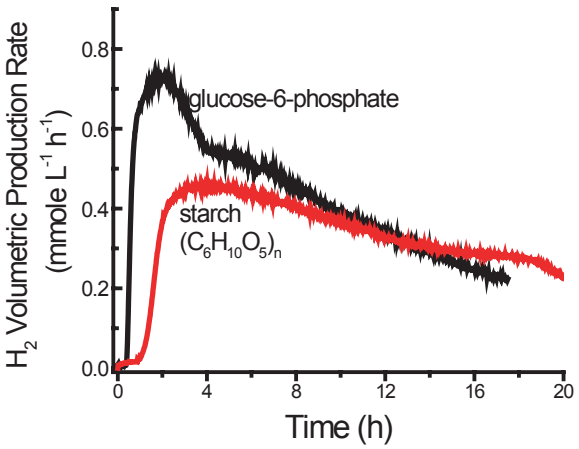

Figure 2. Hydrogen production from either 2 mM G-6-P or 2 mM starch (glucose equivalent). The reaction based on G-6-P contained the pentose phosphate cycle enzymes (#3-12, 1 unit each), ~70 units of *P. furiosus* hydrogenase (#13), 0.5 mM thiamine pyrophosphate, 2 mM $NADP^+$, 10 mM $MgCl_2$, and 0.5 mM $MnCl_2$ in 2.0 ml of 0.1 M HEPES buffer (pH 7.5), at 30°C. The reaction based on starch rather than G-6-P was supplemented by 10 units of α-glucan phosphorylase (#1), 10 units of phosphoglucomutase (#2), and 4 mM phosphate at 30°C.
doi:10.1371/journal.pone.0000456.g002

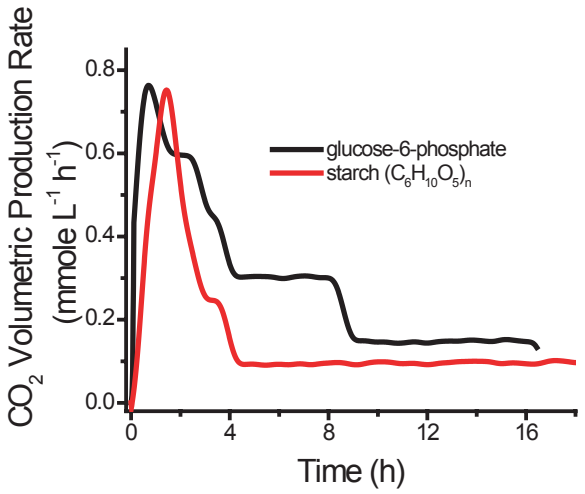

Figure 3. Carbon dioxide production from either 2 mM G-6-P or 2 mM starch (glucose equivalent). The experimental conditions were the same as those in Figure 2.
doi:10.1371/journal.pone.0000456.g003

hydrogen production from starch exhibits a) a longer lag phase, b) a lower peak production rate (0.44 mmol/h/L), and c) an extended reaction time, all of which are consistent with the reaction mechanism (Fig. 1). The CO_2 production for both cases was measured at the same time (Fig. 3). Clearly, CO_2 was produced before H_2 generation, which was in a good agreement with the mechanism in Figure 1. The integrated yields (mol/mol) of hydrogen and CO_2, based on substrate consumption of G-6-P and starch, were 8.35 H_2/G-6-P and 5.4 CO_2/G-6-P, and 5.19 H_2/glucose unit and 5.37 CO_2/glucose unit, respectively. The yields of hydrogen and CO_2 from G-6-P were approximately 70% and 86% of theoretical yields. The corresponding value for hydrogen from starch was lower (43%) although the CO_2 yield was the same. The lower hydrogen yield was anticipated and its causes, such as the unfinished reaction, batch operation, and accumulation of metabolites (e.g., NADPH), are currently under study.

Thermodynamic analysis (Fig. 4) shows that the overall reaction (Equation 1) is a spontaneous process (i.e., $\Delta G^\circ = -48.9$ kJ/mol) and is a weakly endothermic reaction (i.e., $\Delta H^\circ = 595.6$ kJ/mol), based on data elsewhere [21,24]. Since the gaseous products (H_2 and CO_2) are simultaneously removed from the liquid reaction solution, the real Gibbs free energy at 30°C and atmospheric pressure is much less than −48.9 kJ/mol, according to Le Chatelier's principle. The fairly large negative values of Gibbs free energy suggest a complete conversion. Sugar chain-shortening substrate phosphorylation (Eq. 2) utilizes the energy stored in the glucosidic bonds of polysaccharides (15.5 kJ/mol glucosidic bond) to produce the activated phosphorylated monosaccharide (G-1-P) without ATP consumption [20,25] and avoids using expensive substrates such as glucose-6-phosphate [23]. The endothermic reaction suggests that some low-temperature heat energy from the environment is used to produce high quality energy carrier hydrogen, an extra 22% net energy gain. Although photosynthesis efficiency from solar energy to chemical energy is not so high as that of solar cells [26], hydrogen production based on inexpensive abundant biomass will be a shortcut to realization of the hydrogen economy without net carbon emissions, will avoid large capital investments for the hydrogen infrastructure, and will save the huge energy consumption currently required for production of solar cells [3].

DISCUSSION

There are four other means converting biomass to hydrogen: 1) direct polysaccharide gasification [8,13]; 2) direct glucose chemical catalysis after polysaccharide hydrolysis [10,11]; 3) anaerobic fermentations [9,15,18]; and 4) polysaccharide- or glucose-ethanol fermentations [27–29] followed by ethanol chemical reforming [12]. The chemical methods have low hydrogen yields (50∼57%) due to poor selectivity of catalysts and requires high reaction temperatures (e.g., 500∼900 K) [8,10,11,13]. Anaerobic hydrogen fermentation is well known for its low hydrogen yield of 4 H_2/glucose [9,15,18]. The combination of ethanol fermentation and ethanol-to-hydrogen reforming has a theoretical yield of 10 H_2/glucose unit (e.g. 83% of the maximum). Allowing 5∼10% fermentation loss [30] and ∼5% reforming loss [12], the practical hydrogen yield through ethanol could be ca. 75% of the maximum yield. Assembly of the

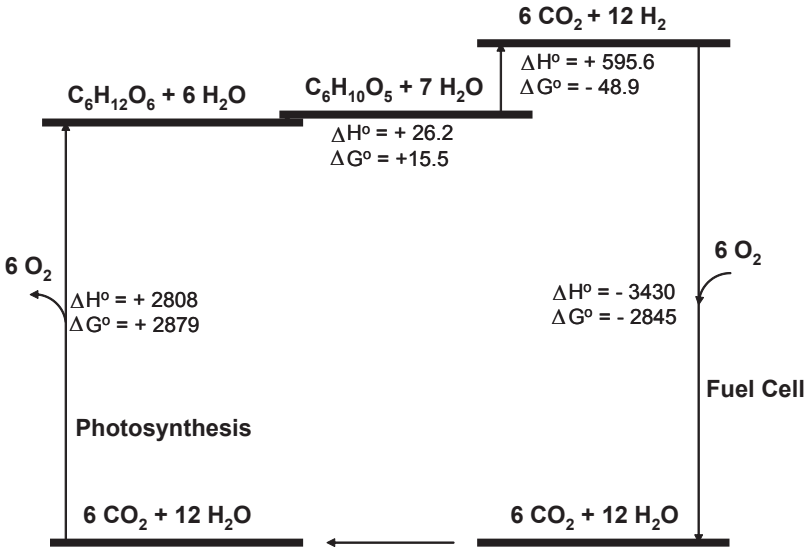

Figure 4. An energy diagram showing the standard enthalpy (ΔH°) and free energy changes (ΔG°) in kJ/mol for the reactions in a renewable energy cycle operating among H_2O, CO_2, glucose, and starch.
doi:10.1371/journal.pone.0000456.g004

high-substrate-selectivity enzymes results in an artificial cascade enzymatic pathway, accompanied by a high hydrogen yield (12 H_2/glucose), three time higher than the theoretical yield (4 H_2/glucose) from biological hydrogen fermentations [9,15,18] and much higher than those from chemical catalysis [8,10,11].

Distinct from the severe reaction conditions of chemical catalysis [8,10–14], the mild reaction conditions mediated by enzymes (~20–100°C, depending on the enzymes employed) provide two obvious benefits: 1) easy implementation in a small space, especially for mobile applications, and 2) simple process configurations due to easy separation of the gaseous products (H_2 and CO_2) from the reactants (starch and water).

Costs of hydrogen production from less-costly starch (e.g., \$~0.15/kg) would be ~\$2/kg H_2, assuming that feedstock costs account for half of overall costs and enzymes and co-enzyme account for another half. In general, approximately 40–75% of prices of commodities, such as gasoline from crude oil, hydrogen from natural gas, and ethanol from corn kernels, come from feedstock costs [31]. For example, current crude recombinant enzyme production costs are estimated to range ~\$10/kg; commercial cellulase production cost is as low as \$1–2/kg [29]. Based on the rule of thumb for commodity production costs, the likely hydrogen-producing costs (~\$2/kg H_2) could meet or exceed the hydrogen cost goals (\$2–3/kg H_2), established by the US DOE [32]. For example, the soaring prices of natural gas drove hydrogen costs from \$1.40/kg H_2 in 2003 to \$2.70/kg H_2 in 2005. We improve the method first described by Woodward [23] by starting with a less costly and abundant substrate–starch. Thus we avoid several major shortcomings of Woodward's method: 1) costly glucose-6-phosphate, 2) accumulation of phosphate, which is a strong inhibitor of fructose-1,6-bisphosphatase, 3) increasing ionic strength in the buffer, which slows down overall reaction rates, and 4) a pH shift in the buffer.

Solid starch has a relatively high energy density, with a mass-storage density of 14.8 H_2-mass % and a volume-storage density of 104 kg H_2/m^3. These densities are higher than most of the solid hydrogen storage technologies [7], as well as exceeding the DOE goals of 4.5 mass%, 6 mass%, and 9 mass% in 2005, 2010, and 2015, respectively [5]. Replacement of conventional solid hydrogen storage technologies by the on-board starch-H_2 converter and starch container will also solve several problems for solid hydrogen storage devices, e.g., energy loss for hydrogen compression or liquefaction, durability of reversible adsorption/desorption materials, high temperatures for desorption, and a long refilling time [5,7]. Easy and safe storage and distribution of solid starch will address many issues of the hydrogen economy infrastructure. For example, setting up the infrastructure to store and distribute gaseous hydrogen to vehicles might cost hundreds of billions in the USA alone [33].

This robust synthetic enzymatic pathway that does not function in nature was assembled by 12 mesophilic enzymes from animal, plant, bacterial, and yeast sources, plus an archaeal hyperthermophilic hydrogenase. The performance (e.g., reaction rate and enzyme stability) is anticipated to be improved by several orders of magnitude by using the combination of (a) enzyme component optimization *via* metabolic engineering modeling [34], (b) interchangeable substitution of mesophilic enzymes by recombinant thermophilic or even hyperthermophilic enzymes [23], (c) protein engineering technologies, and (d) higher concentrations of enzymes and substrates. We have increased the hydrogen production rates by nearly 4 times greater than Woodward's results [23] through a) decreasing the ion strength of the buffer and b) substituting one mesophilic enzyme (#11). This research approach will naturally benefit from on-going improvements by others in synthetic biology systems that are addressing cofactor stability [35], enzyme stability by additives [36], and co-immobilization [37], and development of minimal microorganisms [38] that can be built upon to create an *in vivo* enzyme system that produces H_2 in high yields.

The concept of cell-free synthetic enzymatic pathway engineering is anticipated to be applied to other commodity chemical production because of its unique benefits: high product yields (i.e., no formation of by-products and cell mass), modest reaction conditions as compared to chemical catalysis, no toxic chemicals

Table 1. The enzymes used for hydrogen production from starch and water, and their reaction mechanisms, sources, and amounts used in the reaction.

E.C.	Enzyme Name	Reaction	Vender	Origin	Unit
2.4.1.1	glycogen phosphorylase	$(C_6H_{10}O_5)_n+P_i+H_2O\rightarrow(C_6H_{10}O_5)_{n-1}$+glucose-1-P	Sigma	rabbit muscle	10
5.4.2.2	phosphoglucomutase	G-1-P→G-6-P	Sigma	rabbit muscle	10
1.1.1.49	glucose-6-phosphate dehydrogenase	G-6-P+$NADP^+$→6-phosphogluconate+NADPH	Sigma	*S. cerevisiae*	1
1.1.1.44	6-phosphogluconic dehydrogenase	6-phosphogluconate+H_2O+$NADP^+$→ribulose-5-phosphate+NADPH+CO_2	Sigma	*S. cerevisiae*	1
5.3.1.6	ribose 5-phosphate isomerase	ribulose-5-phosphate→ribose-5-phosphate	Sigma	spinach	1
5.1.3.1	ribulose-5-phosphate 3-epimerase	ribulose-5-phosphate→xylulose-5-phosphate	Sigma	*S. cerevisiae*	1
2.2.1.1	transketolase	xylulose-5-phosphate+ribose-5-phosphate→sedoheptulose-7-phosphate+glyceraldehyde-3-phosphate	Sigma	E. coli	1
		xylulose-5-phosphate+erythrose-4-phosphate→fructose-6-phosphate+glyceraldehyde-3-phosphate			
2.2.1.2	transaldolase	sedoheptulose-7-phosphate+glyceraldehyde-3-phosphate→fructose-6-phosphate+erythrose-4-phosphate	Sigma	*S. cerevisiae*	1
5.3.1.1	triose-phosphate isomerase	glyceraldehyde 3-phosphate→dihydroxacetone phosphate	Sigma	rabbit muscle	1
4.1.2.13	aldolase	glyceraldehyde 3-phosphate+dihydroxacetone phosphate→fructose-1,6-bisphosphate	Sigma	rabbit muscle	1
3.1.3.11	fructose-1,6-bisphosphate	fructose-1,6-bisphosphate+H_2O→fructose-6-phosphate+Pi	[41]	*E. coli*	1
5.3.1.9	phosphoglucose Isomerase	fructose 6-phosphate→glucose-6-P	Sigma	*S. cerevisiae*	1
1.12.1.3	*P. furiosus* hydrogenase I	NADPH+H^+→$NADP^+$+H_2	[22.42]	*P. furiosus*	~70

doi:10.1371/journal.pone.0000456.t001

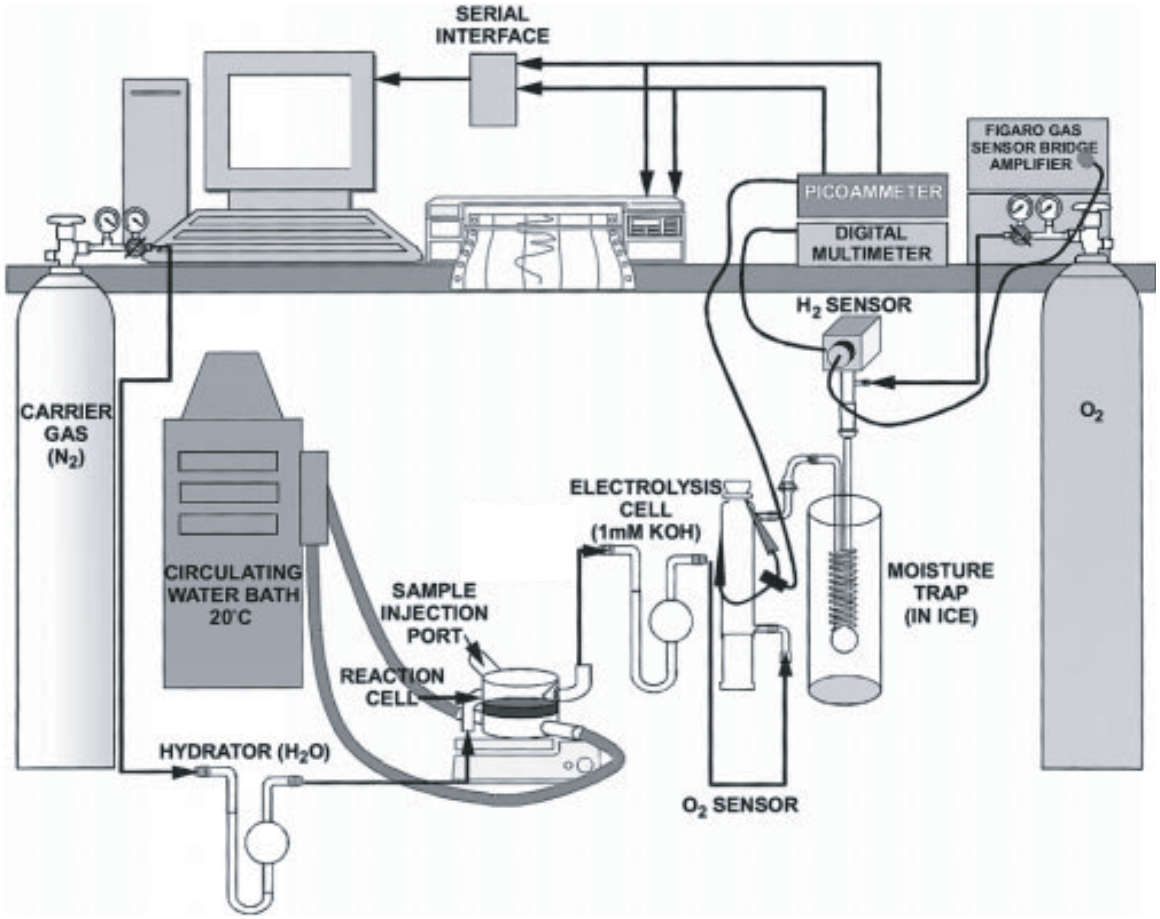

Figure 5. The hydrogen cell system configured for monitoring H_2 with the ORNL in-house sensor based on the Figaro TGS 822 and O_2 with a modified Hersh galvanic cell [43]. The CO_2 analyzer (not shown) is attached between the reaction cell and the electrolysis cell.
doi:10.1371/journal.pone.0000456.g005

required or produced, broad reaction conditions (e.g., high temperature and low pH) as compared with microorganisms, and easy operation and control. For example, it has been argued that cell-free ethanol fermentation systems would replace microbe-based ethanol fermentation someday [39].

With technology development and integration with PEM fuel cells, the starch-to-hydrogen conversion technology is anticipated to have wide mobile applications. We envision that future mobile appliances will store solid starch, produce hydrogen from starch and water via this reaction, and then generate electricity by hydrogen fuel cells at the same compact place.

MATERIALS AND METHODS

All chemicals and enzymes were purchased from Sigma Co, unless otherwise noted. All enzymes and their catalysis reactions are listed in Table 1.

The experiments were carried out in a continuous flow system as described previously [23], with the modification that the moisture traps were cooled with ice instead of liquid nitrogen, and that oxygen as well as hydrogen and carbon dioxide were monitored in the gas stream [23] (Fig. 5). The working volume of the custom reactor was 2 mL. The system was continuously purged with helium at a flow rate of 50 mL/min. The temperature of the jacketed reaction vessel was maintained at 30°C with a Polyscience (Niles, IL 60714) circulating water bath. Hydrogen evolution was measured with a Figaro TGS 822 tin oxide sensor connected over a bridge amplifier to a Keithley Model 2000 multimeter (Keithley Instruments, Cleveland, OH). Oxygen concentration was monitored with a modified Hersh galvanic cell using 24% KOH as the electrolyte connected to a Keithley autoranging picoammeter. Carbon dioxide production was measured with a LI-COR CO_2 Analyzer Model LI-6252 connected to a Keithley 2000 multimeter. The multimeters and picoammeter were connected to a 486 computer through IEEE 488 general-purpose interface boards. Electrolysis for calibration of hydrogen and oxygen by Faraday's law of electrochemical equivalence was carried out with a Keithley 220 programmable current source connected to an in-line electrolysis cell. Calibration for carbon dioxide was carried out with an analyzed gas mixture consisting of 735 ppm carbon dioxide and 1000 ppm oxygen in helium (Air Liquide America Corp., Houston, TX 77056). Data collection and analysis was carried out with ASYST 4.0 software (ASYST Technologies, Inc., Rochester, NY).

The integrated molar/molar yields of hydrogen (Y_{H2}) and carbon dioxide (Y_{CO2}) are calculated as

$$Y_{H2} = \frac{\int r_{H2} dt}{12 * \Delta GE}$$

$$Y_{CO2} = \frac{\int r_{CO2} dt}{6 * \Delta GE}$$

in which r_{H2} and r_{CO2} are the volumetric production rates in terms of mmole of H_2 or CO_2 per liter of reaction volume per hour, as shown in Figs. 2 and 3; $\Delta GE$is the net consumption of glucose equivalent in terms of mM. Residual G-6-P can be measured using Sigma glucose HK kit [40]. The mixtures were incubated at 35°C for 5 minutes and the change in absorbance at 340 nm was determined. In the case of starch, the residual starch, G-1-P, and G-6-P were hydrolyzed to glucose by addition of dilute H_2SO_4 and hydrolysis at 121°C for 1 hour. The neutralized glucose solutions were measured by a glucose HK kit [40].

ACKNOWLEDGMENTS

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Author Contributions

Conceived and designed the experiments: YZ JM. Performed the experiments: YZ BE. Analyzed the data: MA YZ BE. Contributed reagents/materials/analysis tools: YZ RH. Wrote the paper: MA YZ BE JM.

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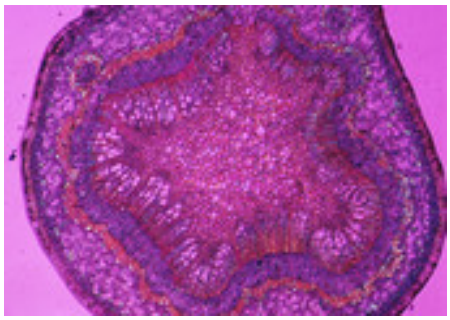
Call for views: Synthetic biology



The Royal Society seeks your views on the emerging area of synthetic biology. This is your opportunity to shape the focus of the Royal Society's future policy work in this important area. We welcome views from individuals or organisations by 27 August 2007. Please see below for submission details.

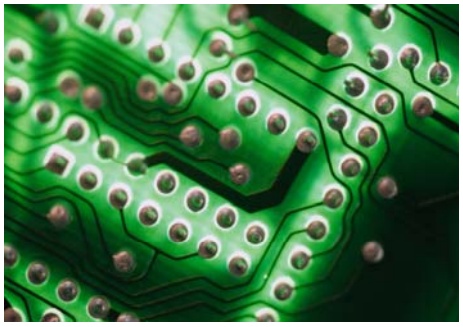
What is synthetic biology?

Synthetic biology is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems.

Biologists have traditionally sought to understand how life works. In contrast, synthetic biologists seek to design and build new biological systems. The application of engineering principles to the design and construction of complex biological systems is likely to provide a step change from the tweaking of existing genomes, usually described as genetic engineering.

The development of standardised technology and methodology for designing and manufacturing semiconductor chips (electronic components) has transformed information and communications technologies (ICTs) over recent decades. The principles of abstraction and modularisation, which underpinned this transformation, are now being applied to the design and construction of biological systems. Parallels have been drawn between the revolution in ICTs and the potential impact of developments in synthetic biology.

Synthetic biologists are seeking to construct standardised biological parts and instructions for assembling these into biological systems. This could eventually lead to the manufacture of novel biological systems and devices that could have applications in a range of areas such as healthcare, energy and the environment.



Synthetic biologists are also constructing a bacterium with the minimal genome required for life. Genes could be inserted to this genome to build biological pathways with functions that have commercial applications. Research is also seeking to extend and rewrite the genetic code to enable the production of proteins that do not occur naturally, but that could have industrial and medical applications. A few potential applications of synthetic biology are outlined below.

Synthetic biology has developed from the convergence of knowledge and tools from other disciplines such as systems biology, genetic engineering, mechanical engineering, electrical engineering, information theory, physics, nanotechnologies and computer modelling. Like most emerging technologies, the boundaries between synthetic biology and other technologies and scientific disciplines are blurred.

Potential applications of synthetic biology

Potential applications of synthetic biology range widely due to the interdisciplinary nature of the field. It could have implications for agriculture, engineering and processing, energy production and the pharmaceutical industry. A few examples of potential applications include:

- ***Development of a cheap anti-malarial drug –*** The plant derived drug has a high success rate in treating malaria, but has been impractical and costly to produce by standard chemical methods. By building a new metabolic pathway in yeast and *E coli* with genes from three separate organisms, researchers have created a
- bacterial strain that can produce amorphadiene. This precursor can then be converted into artemisinin. It is hoped that the drug could be available in the next few years.
- ***The beginning stages of a cheap and green, high yield hydrogen production*** – Hydrogen could become an important alternative to fossil fuels. A novel synthetic pathway consisting of 13 enzymes derived from five different organisms has been developed to produce hydrogen from starch and water. This pathway is being developed further with the aim of producing hydrogen from cellulose, a more abundant sugar, which could provide hydrogen for fuel cells cheaply and easily.
- ***Looking for an answer to environmental contamination*** – Communities of micro organisms are responsible for most naturally occurring biodegradation. The metabolic and genetic control mechanisms of these organisms could provide clues to create and develop novel micro organisms to decontaminate the most potent environmental contaminants.
- ***Programmable cells for use in gene therapy*** – Pathogenic bacteria and viruses are able to identify and manipulate cells to produce harmful affects. Programming a bacterium or virus that can identify malignant cells and deliver a therapeutic agent could have major benefits for treating cancer and similar illnesses.

Call for views

This is your chance to shape the focus of the Royal Society's future policy work in this area. This work could take a number or forms, such as a substantial policy study or a stakeholder workshop.

Synthetic biology has the potential to lead to a wide range of useful applications, but it also raises a number of uncertainties including its possible impact on society. There has been some discussion around the social, ethical and legal issues that synthetic biology may present and the Society is keen to encourage a wider constructive discussion and debate about these issues. We are hoping to receive comments and information from a range of stakeholders on both the opportunities and uncertainties that could accompany the development of synthetic biology.

We would like to receive submissions commenting on any aspects of synthetic biology and would be pleased to hear suggestions on particular areas or issues that the Society should focus on when deciding what work to undertake in this area. Broad topics that you may wish to comment on are listed below. There is no need to comment on all these areas, and we welcome comments on subjects other than those listed:

- Potential developments and applications
- Current research capacity and geographical distribution
- Societal implications
- Ethical concerns
- Biosecurity risks
- Implications for the environment
- Research support and funding
- Implications for human health
- Legal issues and implications for regulation (national and international)
- Ownership, sharing and innovation frameworks (including intellectual property)
- Biosafety concerns
- Education and training
- Governance and oversight of research
- Economic considerations for developed and developing countries

We would be happy to receive electronic copies, links to electronic copies, or hard copies of relevant reports and references.

Submissions

The deadline for submissions is **27 August 2007**, either electronically (preferred format) or by post to:
E-mail synthetic.biology@royalsoc.ac.uk
Post Kate O'Shea, Science Policy, The Royal Society, 6-9 Carlton House Terrace, London SW1Y 5AG, UK

Responses are likely to have the greatest impact if they are restricted to four pages, plus appendices if appropriate.

Confidentiality

A list of organisations and individuals who have submitted views will be listed in our website and the submissions may be published. Please inform us if you **do not** want your name or your submission to be made public. If you are submitting information on behalf of an organisation, please include details of the relevant person to contact should we wish to discuss issues raised in your submission.

If you would like to submit your views but are unable to meet the deadline, or if you have any questions, please contact us on the details above.

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The Royal Society is the independent scientific academy of the UK and the Commonwealth, dedicated to promoting excellence in science. As well as providing an authoritative voice and leadership for UK science, it aims to ensure that policies on key issues are influenced by the best independent science and it provides advice for policymakers on science and its relationship with society.

The Royal Society is committed to encouraging the responsible development of new and emerging technologies for the maximum benefit of humanity and the environment. It is well placed to provide an expert, independent and realistic assessment of the risks, benefits and impacts that new and emerging technologies could present. The Society has undertaken projects on a wide range of scientific areas, including nanotechnologies. For more information on our policy work, visit www.royalsoc.ac.uk/policy.

Please circulate this document to other interested parties.

A sweet out-of-the-box solution to the hydrogen economy: is the sugar-powered car science fiction?

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The hydrogen economy presents a compelling future energy picture, especially for the transportation sector. The obstacles, such as low-cost hydrogen production, lack of high-density hydrogen storage approaches, costly infrastructure, and safety concerns are prohibiting its large-scale implementation. To address the above challenges, we propose a new solution – use of starch or cellulose ($C_6H_{10}O_5$) from biomass as a hydrogen carrier. This new solution is based on the invention of complete conversion of glucans (starch and cellulose) and water to hydrogen and carbon dioxide as $C_6H_{10}O_5$ (aq) + $7H_2O$ (l) → $12H_2$ (g) + $6CO_2$ (g). The production of hydrogen from carbohydrates is a nearly carbon-neutral process based on the whole carbon cycle. The use of low-cost renewable carbohydrate as a high hydrogen density carrier (14.8 H_2 mass %) may solve problems such as hydrogen production, storage and distribution, as well as address safety concerns. Increasing hydrogen generation rate (power density) and decreasing costs are two major tasks prior to this technology's wide implementation. Analysis based on past scientific knowledge and technical achievements suggests that sugar-powered vehicles could become real in the future with intensive R&D efforts. Here we are calling for international R&D collaborations to pursue the holy grail of the carbohydrate hydrogen economy.

1. Introduction

Human society has smoothly passed through two transportation energy revolutions from animal forces relying on living plant biomass to external combustion engines (steam engines) driven by solid coal to internal combustion engines (ICE) driven by liquid gasoline and diesel.[1] Transportation ability often reflects civilization level. Without it, cities could not exist; families would have to live close to the land, gathering and growing their own food; materials, medicines, medical cares, manufacturing, and electricity generation all depend on transportation.[2]

Currently, liquid fuels (gasoline, diesel, and jet fuel), along with internal combustion engines, are widely used to propel vehicles, trains, ships, and jet planes because of several advantages: (1) relatively low fuel prices (until more recently); (2) very high energy storage densities (MJ per kg of fuel and MJ per litre of fuel); (3) high power density (kW per kg of engine); (4) easy storage, distribution, transportation, and refilling for liquid fuels; (5) relatively low costs for ICE ($ per kW of output); and (6) safety for mass utilization. But the concerns pertaining to soaring prices of crude oil, depleting fossil fuels, net CO_2 emissions, climate change, national energy security, global and local food security, (rural) economic development, energy utilization efficiency, and wealth transfer are motivating the development of sustainable alternative transportation fuels. Second generation biofuels such as cellulosic ethanol, butanol, algae biodiesel, hydrocarbons, and synthetic diesel, can be integrated well with current infrastructures for liquid fuels and ICE systems but the ICE systems have relatively low energy efficiencies, since the efficiencies of heat engines are restricted by the second law of thermodynamics.

In the long term, improving energy utilization efficiency through hydrogen-fuel cell/electricity systems will be vital for sustainable transportation. Distinct from first generation fuels (*e.g.*, solid coal) and second generation fuels (*e.g.*, liquid gasoline,

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Broader context

Synthetic biology is an emerging interdisciplinary area that combines science and engineering in order to design and build novel biological functions and systems. Cell-free synthetic biology through *in vitro* assembly of a number of enzymes and coenzymes has been designed to implement unnatural reactions as $C_6H_{10}O_5$ (aq, starch or cellodextrins) + 7 H_2O (l) → 12 H_2 (g) + 6 CO_2 (g). This new sugar-to-hydrogen technology promises to address several obstacles to the hydrogen economy – cheap hydrogen production, high hydrogen storage density (14.8 H_2 mass%), and costly hydrogen infrastructure, and to eliminate safety concerns about mass utilization of hydrogen. Also, these reactions can produce more chemical energy output as hydrogen than chemical energy input stored in polysaccharides for the first time.

diesel), third generation transportation fuels include hydrogen and electricity, both of which work as energy carriers that can be converted to kinetic work efficiently without the restriction of the second law of thermodynamics. Both hydrogen and electricity will be generated from various primary energy sources, such as biomass, solar energy, wind energy, geothermal energy, tidal energy and so on. The hydrogen-fuel cell-electricity system will play a predominant role because of (1) very high energy conversion efficiency through fuel cells, (2) minimal pollutants generated, (3) much higher energy storage densities than rechargeable batteries alone, and (4) diverse hydrogen-producing means from primary energy resources. But large-scale implementation of the hydrogen economy must break four technological hurdles – low cost hydrogen production from any primary energy resources, high hydrogen density storage means (>9 mass%), affordable fuel distribution infrastructure, and affordable fuel cells throughout the whole life cycle.[3–5] In addition, hydrogen is a flammable, odorless, colorless gas. Any significant hydrogen explosion accident could prevent the public from accepting hydrogen as a transportation fuel.

Transportation fuels are and will be mainly produced by four primary resources – crude oil, natural gas, lignocellulosic biomass, and starchy crops like corn. Based on energy contents ($ per gigajoule, GJ), delivered lignocellulosic biomass at $60 per dry ton ($3.60 per GJ) is least costly among all primary energy sources – compared to natural gas ($7.58 per GJ, $8 per mbtu), crude oil ($15 per GJ, $80 per barrel), and corn kernels ($13 per GJ, $4.5 per bushel) (Fig. 1). Although coal energy content ($1.54 per GJ, $50 per ton) is lower than that of lignocellulosic biomass, the conversion of coal to liquid transportation fuels is economically and environmentally prohibitive, except in special times or areas (*e.g.*, Germany during World War II and South Africa).

Comparison of different current and potential transportation fuels is very complicated, involving a number of factors – fuel costs, resource availability, infrastructure availability, costs and lifetime of the engine/motor, environmental impacts, *etc*. Direct price comparison of transportation fuels, such as gasoline, diesel, ethanol, biodiesel, methanol, hydrogen, or even electricity, is relatively straightforward for end-users because their prices include costs associated with feedstock, processing, capital depreciation, distribution, profits, and taxes. Fig. 1 shows the energy contents of potential fuels in an increasing order from carbohydrate ($10.6 per GJ, $0.18 per kg), electricity ($16.7 per GJ, $0.04 per kWh), methanol ($17.8 per GJ, $0.35 per kg), gasoline ($17.6 per GJ, $2.5 per gallon), diesel ($19.5 per GJ, $2.7 per gallon), ethanol ($22.1 per GJ, $2 per gallon), hydrogen ($25.0 per GJ, $3 per kg), to biodiesel ($27.4 per GJ, $3.5 per gallon). Carbohydrates isolated from corn kernels, sugarcane or cellulosic materials will be the least costly. Further conversion of carbohydrates to other fuels, such as ethanol, hydrogen or even synthetic bio-oil, will lead to higher prices. Electricity, a universal energy currency, can be generated from a number of resources – coal, natural gas, wind energy, nuclear energy, hydroelectric energy, and so on. Regardless of its generation means, electricity prices vary in a relatively narrow range after numerous conversions and grid distribution.

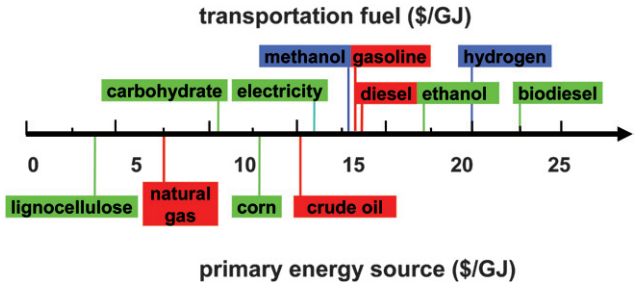

Fig. 1 Cost comparison of primary energy resources and potential transportation fuels. The prices of energy resources and fuels vary in a relatively large range and the values only represent likely recent prices.

In this perspective, we briefly review the challenges for the hydrogen economy, propose an out-of-the-box solution that could systematically solve several of these challenges, discuss its technical feasibility, and emphasize future research directions.

2. The hydrogen economy

The hydrogen economy will be a linked network of processes that produces hydrogen, stores hydrogen chemically or physically, and converts the stored hydrogen to electrical energy at the point of use.[3,6–8] Hydrogen is advantageous over electricity stored in rechargeable batteries for the transportation sector because stored hydrogen has a ~20-fold to >100-fold higher energy storage density than electricity stored in rechargeable batteries in terms of GJ per kg.[9,10] Battery-only electric vehicles have a much shorter driving distance per recharging than hydrogen fuel cell systems.

Hydrogen can be produced from water and other hydrogen-containing compounds such as CH_4 and carbohydrates by a number of chemical, biological, electrical, photochemical, and-photobiological approaches. Most hydrogen is currently produced from natural gas by a combination of steam reforming and water shift reactions, accompanied with a net release of CO_2 to the atmosphere. Because of soaring prices of fossil fuels, hydrogen production costs were more than $2.70 per kg of hydrogen in 2005;[11] a situation that has clearly deteriorated since then.

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Gaseous hydrogen storage is still the largest challenge. It can be stored (1) in high-pressure gas cylinders; (2) as liquid hydrogen in cryogenic tanks (at 21 K); and (3) in solid forms (*e.g.*, adsorption on large specific surface area solid materials or hydrides (*e.g.*, $LiAlH_4$, $NaAlH_4$, $NaBH_4$) or by the reaction of light metals and water.[4,12] As for approaches 1 and 2, considerable energy is lost in hydrogen compression (~10–15%) or hydrogen liquefaction (~33%). Both also have low hydrogen storage densities, for example, liquid hydrogen has a hydrogen density of only 70.8 kg/m^3 (*i.e.*, less than 7 mass H_2%). Generally speaking, large scale high-pressure and cryogenic hydrogen storage systems are impractical for vehicular application due to safety concerns and volumetric constraints.[13] Solid hydrogen storage technologies require high-gravimetric hydrogen density, adequate hydrogen-dissociation energetics, or stable and low-cost hydrogen carriers.[12,13] Therefore, the US Department of Energy (DOE) set hydrogen storage goals at 6 mass% and 9 mass% for 2010 and 2015, respectively.[5] Recently, possible hydrogen-storage materials meeting FreedomCar requirements (*e.g.*, density, refilling rate, refilling time, and reuse cycle time), such as metal-organic frameworks with potential densities of 10 H_2 mass%, have been proposed in the DOE 2008 annual merit review and peer evaluation.[14]

Hydrogen, a small and energetic molecule, can diffuse through container materials or react with materials. For example, hydrogen cannot be simply delivered by today's natural gas pipeline systems because of steel embrittlement, accompanied with increased maintenance costs, leakage rates, and material replacement costs. Hydrogen pipelines will be much more expensive than electric transmission lines and natural gas pipelines. Proponents of the hydrogen economy propose local hydrogen stations based on local sources.[15,16] Unfortunately developing these stations in high demand urban areas will have many challenges, including NIMBY (not in my backyard) backlash. Finally, a huge investment in the infrastructure is required for storing and distributing hydrogen, costing at least one trillion of dollars in the USA alone.[15,17]

In order to solve the challenges associated with gaseous hydrogen storage and costly infrastructure, high-energy-density liquid fuels – such as methanol, ethanol, liquefied petroleum gas, gasoline, or biodiesel – have been proposed as hydrogen carriers. The vehicles must have an onboard chemical converter to reform them to hydrogen. Methanol, a liquid fuel, can be converted to hydrogen very easily *via* reforming or can be converted to electricity through direct methanol fuel cells (DMFC). The challenges faced by the DMFC technology include methanol crossover, high catalyst costs, low power density, poor efficiency, and short operation life.[18–20] Ethanol and hydrocarbons can be converted to hydrogen and CO_2 plus some CO *via* catalytic steam reforming, partial oxidation, or auto-thermal reforming.[21,22] Since a small amount of CO as a side-product of chemical catalysis can poison the catalysts of proton exchange membrane (PEM) fuel cells,[22] extra purification steps are required to remove CO before entering PEM fuel cells. Carbon monoxide clean-up can be done in several ways – water gas shifting, selective CO removal, methanation, and Pd alloy membranes.[21] These reformers have been shown to be highly complicated, difficult to operate, bulky, and expensive.[23] In order to avoid CO poisoning, ammonia, an easily-liquefied carbon-free gas, has been proposed as a hydrogen carrier. Production of NH_3 from pure hydrogen and the consequential conversion of ammonia to hydrogen is not energy- and cost-efficient. Obviously, any current high-temperature on-board reformers result in system complexity and some energy loss during such conversions, implying their infeasibility for vehicular applications.

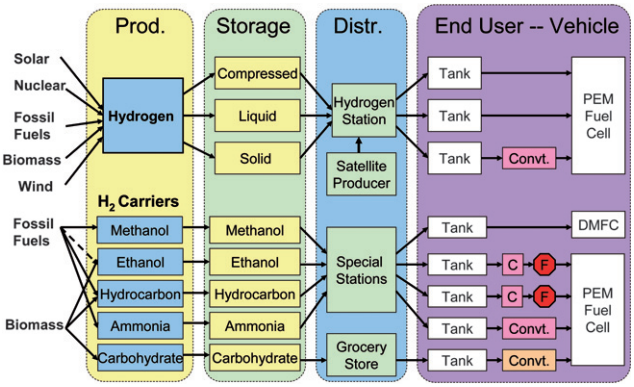

Fig. 2 Comparison of the different scenarios of the hydrogen economy.

Low-temperature PEM fuel cells are used primarily for transportation applications due to their fast startup time, low sensitivity to orientation, high energy conversion efficiency, low-operating temperature (below 100 °C), and favorable power-to-weight ratio (lightweight and compact). In contrast, high-temperature fuel cells are not amenable to transportation propulsion.[24] Therefore, nearly all the major automakers have fuel cell projects based on PEM technology with an electric motor, but the challenge of gaseous hydrogen storage results in a shorter driving range compared to gasoline-powered vehicles (300–400 miles driving distance per tank). In contrast, the Nobel Prize winner George A. Olah advocates the methanol economy,[25] but DMFC may be good only for low power applications, such as portable electronics.[19]

Fig. 2 presents different possible scenarios of the future hydrogen economy for the transportation sector, including hydrogen production, storage, distribution, fuel cell, and end users – vehicles. Hydrogen can be produced from diverse primary energy sources, such as solar energy, biomass, fossil fuels, tidal energy, geothermal energy, and so on. Once gaseous hydrogen is produced, its storage and distribution will lead to big challenges, as described above. The use of hydrogen carriers, such as methanol, hydrocarbons, or even ammonia, may be more promising in principle than direct use of gaseous hydrogen. But the system complexity of CO removal from the thermal reformers is a show stopper for the carbon-containing hydrogen carriers through on-board reforming. Therefore, the demonstration vehicle systems based on liquid hydrocarbon on-board reforming systems followed by PEM fuel cells have been abandoned. We propose a new solution – the on-board carbohydrate-to-hydrogen-PEM fuel cell system (Fig. 2).

3. An out-of-the-box solution for the hydrogen economy

We propose solid polymeric carbohydrates ($C_6H_{10}O_5$, 14.8 H_2 mass%) as a hydrogen carrier, based on the new *in vitro* synthetic

biology approach.[26] The use of low-cost, sustainable biomass as the primary energy source for producing transportation fuels (*e.g.*, cellulosic ethanol and hydrogen) provides benefits to the environment, economy, and national security.[1,6,27–38] Biomass is an enriched chemical energy source that can solve the scale-up and storage challenges associated with low-power density solar radiation.[39] A number of biomass-to-hydrogen production approaches have been investigated previously:

1. gasification,[40,41] (fast or flash) pyrolysis,[42–46] or aqueous phase reforming;[47–51]

2. anaerobic hydrogen fermentation[8,31,52–57] and/or a bio-electrochemically assisted microbial fuel cell reactor that can convert acetate to hydrogen with the help of a little electricity;[58,59]

3. cell-free synthetic enzymatic pathways;[26,60] and

4. combinatorial biological and chemical catalysis: polysaccharide hydrolysis[31,38,61,62] and glucose–ethanol fermentation or consolidated bioprocessing[31,63–65] followed by chemical catalysis – ethanol partial oxidation reforming.[22,66]

The carbohydrate-to-hydrogen conversion by the cell-free synthetic enzymatic pathways (a new *in vitro* synthetic biology approach) features (i) mild reaction conditions, (ii) no CO side-product, (iii) complete conversion, and (iv) potentially high reaction rates. This allows us to propose an out-of-the-box solution for the hydrogen economy: the use of sugars as a hydrogen carrier. Potential applications include stationary power providers, local hydrogen stations, refillable sugar batteries, sugar-powered automobiles, air-independent-propulsion submarines, or even electric aircraft.

3.1. Novel hydrogen production

The novel synthetic enzymatic pathways have been designed to produce 12 moles of hydrogen per mole of glucose equivalent of glucans (starch and cellulose) and water.[26,60] The idea is to utilize the energy stored in polysaccharides to split water and stepwise release all energy of carbohydrates in the form of hydrogen under mild reaction conditions ($\ll$ 100 °C and ~1 atm) as below

$$C_6H_{10}O_5\ (aq) + 7H_2O\ (l) \rightarrow 12H_2\ (g) + 6CO_2\ (g) \qquad (1)$$

These synthetic catabolic pathways that do not exist in nature are comprised of 13 enzymes in one pot (Fig. 3). Most of the reactions in the pathway catalyzed by the enzymes are reversible. The removal of gaseous products from the aqueous phase favors the unidirectional overall reaction. In addition, enzymatic biochemical reactions are well-known for their 100% selectivity at modest reaction conditions. Thermodynamic analysis suggests that the overall reaction is a spontaneous process (*i.e.*, $\Delta G^\circ = -49.8$ kJ mol^{-1}) and is an endothermic reaction (*i.e.*, $\Delta H^\circ = 598$ kJ mol^{-1}).[60] The negative value of Gibbs free energy at 25 °C suggests a nearly complete conversion. The Gibbs energy of this reaction decreased greatly with an increase in temperature, suggesting higher conversion at elevated temperatures. This reaction is driven by entropy gain rather than enthalpy loss. Another well-known entropy-driven reaction is acetate fermentation from glucose [$C_6H_{12}O_6$ (aq) + 2 H_2O (l) → 2 CH_4O_2 (aq) + 2 CO_2 (g) + 4 H_2 (g)]. In addition, the removal of both gaseous products from the aqueous reactants at mild reaction condition (< 100 °C and ~1 atm) drives the reaction forward to completion.[60] This entropy-driven chemical reaction can generate more output chemical energy in the form of hydrogen than input chemical energy in polysaccharides by adsorbing ambient-temperature thermal energy.[26,60]

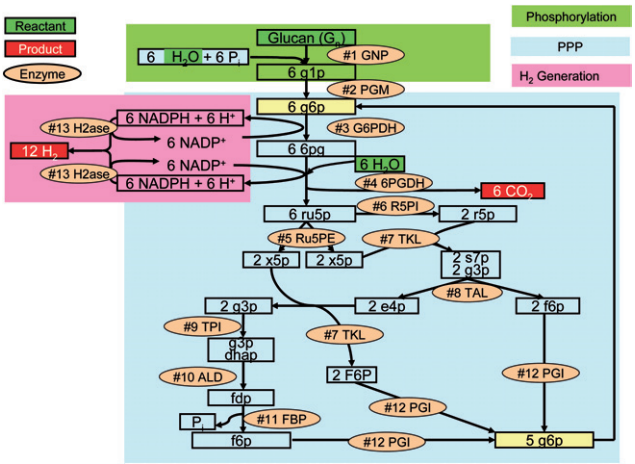

Fig. 3 The synthetic metabolic pathway for complete conversion of glucan and water to hydrogen and carbon dioxide. PPP, pentose phosphate pathway taken from ref. 26. The enzymes are: #1 GNP, glucan phosphorylase; #2 PGM, phosphoglucomutase; #3 G6PDH, G-6-P dehydrogenase; #4 6PGDH, 6-phosphogluconate dehydrogenase; #5 R5PI, phosphoribose isomerase; #6 Ru5PE, ribulose 5-phosphate epimerase; #7 TKL, transketolase; #8 TAL, transaldolase; #9 TPI, triose phosphate isomerase; #10 ALD, aldolase; #11 FBP, fructose-1,6-bisphosphatase; #12 PGI, phosphoglucose isomerase; and #13 H_2ase, hydrogenase. The metabolites and chemicals are: g1p, glucose-1-phosphate; g6p, glucose-6-phosphate; 6pg, 6-phosphogluconate; ru5p, ribulose-5-phosphate; x5p, xylulose-5-phosphate; r5p, ribose-5-phosphate; s7p, sedoheptulose-7-phosphate; g3p, glyceraldehyde-3-phosphate; e4p, erythrose-4-phosphate; dhap, dihydroxacetone phosphate; fdp, fructose-1,6-diphosphate; f6p, fructose-6-phosphate; and P_i, inorganic phosphate.

The first proof-of-principle experiment has been conducted to validate whether or not hydrogen can be produced from starch and water.[26,67] A number of enzymes, isolated from animal, plant, bacterial, and yeast sources, plus an archaeal hyperthermophilic hydrogenase, are put together in one pot. Although each of them has a different optimal pH, temperature, and cofactor, the compromised conditions used are 0.1 M HEPES buffer (pH 7.5) containing 5 mM thiamine pyrophosphate, 4 mM phosphate, 2 mM $NADP^+$, 10 mM $MgCl_2$, and 0.5 mM $MnCl_2$ at 30 °C. Under these conditions, each enzyme remains active but is believed to be far from its optimal activity. The first reaction mediated by substrate phosphorylases plays an important role in producing glucose-1-phosphate by shortening polysaccahrides without the use of ATP.[26,63,68,69] Utilization of substrate phosphorylase enzymes is far superior to any kinase reaction involving hexokinase and ATP because of (1) no costly ATP regeneration system; (2) no accumulation of phosphate, an inhibitor of several enzymes (*e.g.*, fructose biphosphatase);[70] (3) no Mg^{2+} precipitation,[70] since Mg^{2+} is a key co-factor of several enzymes; and (4) a more homostatic pH.

Fig. 4 shows that hydrogen is produced as expected, a little later than CO_2 evolution, consistent with the designed mechanism in Fig. 3. A lag phase of hydrogen production is attributed

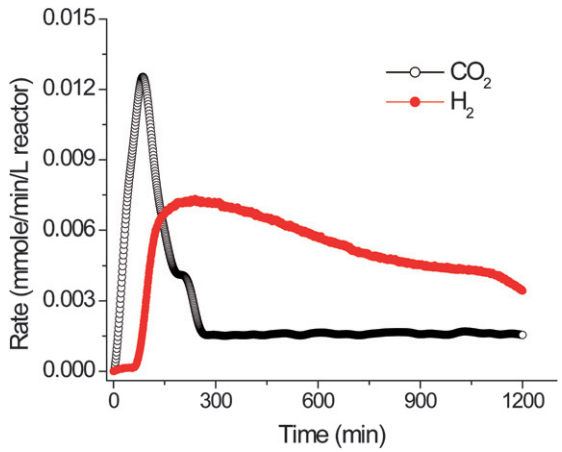

Fig. 4 Hydrogen production from starch and water at 30 °C and 1 atm modified from the ref. 26.

to the initial addition of $NADP^+$ as a cofactor. When NADPH is used, there is no lag phase for hydrogen generation. This proof-of-principle experiment has been conducted by using off-the-shelf enzymes without any optimization so that the reaction rates are very low, far from the demands of practical applications.[26] Recently, the hydrogen production rate has been increased by 8.2 fold starting from cellulosic materials as compared to the previous results by (i) increasing the rate-limiting hydrogenase concentration, (ii) increasing the substrate concentration, and (iii) elevating the reaction temperature slightly from 30 to 32 °C (Table 1). Under the current system parameters, the measured production rate of H_2 is higher than those for photobiological systems and comparable to those reported for dark fermentations.[54] Further enhancement in hydrogen production rates will be discussed in Section 4.

3.2. Special features

The complete conversion of sugars and water to hydrogen and carbon dioxide mediated by these synthetic enzymatic pathways[26,60] provides a number of special features suitable for mobile PEM fuel cells.

1. Highest energy efficiency. Enzymatic hydrogen production is the only one that can produce nearly 12 moles of hydrogen per mole of glucose equivalent. In addition to extracting all the chemical energy stored in the substrate sugars, the overall reaction is endothermic, *i.e.*, some of low-temperature thermal energy is absorbed and converted to chemical energy in the form of hydrogen (22% combustion energy gain during this bioreforming).

2. High hydrogen storage density. Polysaccharides have a chemical formula $C_6H_{10}O_5$ with a reaction of $C_6H_{10}O_5$ (aq) + 7 H_2O (l) → 12 H_2 (g) + 6 CO_2 (g). As a result, hydrogen storage density in polysaccharides is 24/162 = 14.8 H_2 mass%, where water can be recycled from PEM fuel cells.

3. Mild reaction conditions (≪100 °C and ~1 atm), which do not require bulky, costly pressure reactors. The reactor temperatures are at the same range of those of PEM fuel cells, good for coupling these endothermic and exothermic reactions.

4. Nearly no costs for product separation (gas/liquid). This reaction only produces two gaseous products – CO_2 and hydrogen. Under mild reaction conditions, the reactants (sugar and water) plus the enzymes and the cofactor remain in the aqueous phase. Separation of the gaseous products and aqueous reaction is easy and nearly cost-free. Critically, the removal of the reaction products also drives the reactions forward and avoids product inhibition.

5. Clean products for PEM fuel cells along with easy power system configuration.

6. Simple and safe distribution and storage of solid sugars. Therefore, investment for upgrading infrastructure and distribution of solid sugars would be minimal.

3.3. Future applications

These enzymatic sugar-to-hydrogen reactions have several potential applications from local hydrogen generation stations to low-cost electricity generators, to high energy-density batteries, as well as sugar-powered vehicles, all of which require faster hydrogen production rates as this nascent technology is improved and optimized.

3.3.1. Local hydrogen generation station. Gaseous hydrogen distribution infrastructure is not currently available and would be very costly. Local production of hydrogen based on local renewable resources is believed to be a valuable alternative for supplying hydrogen to local end users – hydrogen fuel cell vehicles. Local satellite hydrogen generation stations could produce hydrogen based on this sugar-to-hydrogen approach, store the hydrogen, and refill hydrogen-fuel cell vehicles. The solid sugar powders produced locally will be easily collected and distributed based on current solid goods delivery systems. It is estimated that a several-fold increase in current hydrogen production rates would be sufficient for this application.

Table 1 Summary of enzymatic hydrogen production rates

Substrate	Concentration[a]/mM	Temperature/°C	$V_{max,H2}$/mmole h^{-1} L^{-1}	References
G-6-P	2	30	0.21	140
G-6-P	2	30	0.73	26
Starch	1	30	0.48	26
Cellobiose	2	32	0.48	60
Cellopentaose	8	32	3.92	60

[a] potential glucose equivalent for hydrogen production.

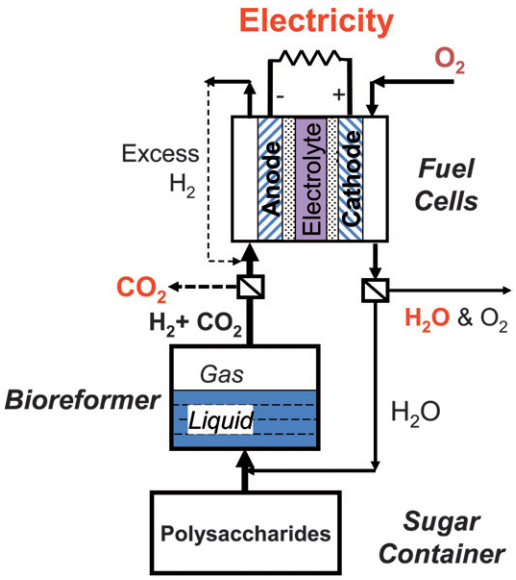

Fig. 5 Conceptual sugar-to-electricity system.

3.3.2. Low-cost (remote) electricity generator. Integration of this sugar-to-hydrogen system with fuel cells (Fig. 5) could produce low-cost electricity from low-cost sugars ($0.18 per kg, Fig. 1), especially ideal for remote areas without electrical transmission lines and grids. The products (hydrogen and carbon dioxide) will bubble up from the aqueous reactants; pure hydrogen could be separated from CO_2 by using alkali adsorption for CO_2 sequestration, pressure swing adsorption or membrane separation; electricity will be generated by fuel cell stacks by using hydrogen and oxygen in the air. The reaction product water of fuel cells will be partially recycled for sugar dissolution. The whole system will have very high electricity conversion efficiencies since the conversion of carbohydrate to hydrogen is endothermic, *i.e.*, 22% of the combustion enthalpy of hydrogen comes from ambient thermal energy or waste heat from fuel cells. If phosphoric acid fuel cells are chosen, hot water will be co-generated. The whole energy (electricity and heat) conversion efficiency may be very close to 100%. It is estimated that a 1 kW electricity generator would have a 60 L bioreformer if a 10-fold increase in hydrogen rate is achieved. With technology improvements, the proposed enzymatic hydrogen production systems will even compete with diesel-to-electricity generators, while avoiding the use of fossil fuels and emitting no net greenhouse gases.

3.3.3. Sugar-powered vehicle. Fig. 6 shows a conceptual sugar-powered vehicles based on a hybrid of PEM fuel cells and rechargeable batteries. This combination will have both high energy storage density and power density. Solid sugar powders will be refilled into the sugar container in the car at local sugar stations; the on-board bioreformer will convert the sugar solution to hydrogen and carbon dioxide by the stabilized enzyme cocktail; a small-size buffer hydrogen storage container will balance hydrogen production/consumption; feeding of a mixture of CO_2/H_2 or pure hydrogen in the PEM fuel cells will dramatically decrease system complexity and greatly increase the system operation performances; approximately a half of water generated

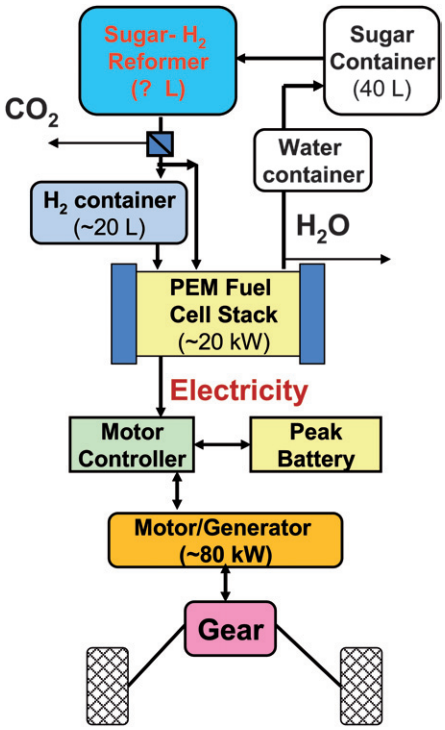

Fig. 6 Conceptual hybrid power train system including on-board sugar-to-hydrogen converter, PEM fuel cell and rechargeable battery.

from the fuel cells is used for dissolving solid sugars. Similarly, the heat output from PEM fuel cells will be coupled to the heat input needed by the bioreformer. The electrical energy from the fuel cells will be sent to the motor controller/motor/gear to generate kinetic energy. When extra energy is needed for acceleration or start-up, electrical energy stored in the rechargeable peak battery will be released. Also, similar to the gasoline-electric hybrid system, *e.g.*, the Toyota Prius, the kinetic energy on braking will be converted to electricity and stored in the battery.

Small-size hydrogen fuel cell vehicles need hydrogen production rates of ~1–2 kg per hour. Producing sufficient hydrogen at rapid rates from a small bioreformer is the number one technological challenge. Producing one kg of hydrogen per hour will need a reaction volume of 130 m^3 based on the current reaction rate of 3.92 mmole of hydrogen per hour per litre, implying that this application is technically impractical. But we expect to be able to increase the hydrogen production rate by several orders of magnitude through a combination of known technologies (see Section 4). To our knowledge, the highest biohydrogen production rate is 21.8 moles of hydrogen per litre per hour,[71] ~5600 times higher than the enzymatic hydrogen process.[60] If we can increase the rate by 2000-fold, the volume of the bioreformer will be as small as 65 litres, which will be small enough to replace small-size internal combustion engines. If 4–10 kg of hydrogen is needed for driving more than 300 miles before refilling, that means that 27–67.6 kg of sugar will be stored in the vehicles, occupying a volume of 38.6–96.6 litres or 10.2–25.5 gallons.

The proposed power train systems would have a very high energy conversion efficiency (overall, 55%; carbohydrate–hydrogen, 122%; hydrogen–PEM fuel cell, 50%; electricity–motor, 90%), ~3.0 times higher than that of ethanol-internal

combustion engines (overall, 18.2%; carbohydrate–ethanol, 90%; internal combustion engine, 25%; transmission, 85%). This proposed energy efficiency would be the highest among all power-train systems, including internal combustion engines, standard hydrogen-fuel cell systems, gas turbines, *etc*. If the USA's biomass resource through bioethanol-internal combustion engines replaced 30% of transportation fuels in 2030,[72] the same amount of biomass through hydrogen–PEM fuel cell systems would achieve at least 90% transportation fuel independence through this new technology without reliance on any other energy sources.

Seemingly competitive technology –aqueous phase reforming[47–51] – is not suitable for on-board PEM fuel cell systems because it has poor hydrogen selectivity, low yield, and dirty products (*e.g.*, CO), and requires high temperature (~250 °C) and pressure (*e.g.*, ~50 atm) reactors. Therefore, on-board reformation though aqueous phase reforming appears not to be technically feasible. Similar situations occur with on-board hydrocarbon-to-hydrogen reforming.

3.3.4. Super-high energy density sugar battery. The system integrating the sugar container, sugar-to-hydrogen reformer with PEM fuel cells can be regarded as a new biodegradable primary battery or refillable (rechargeable) secondary battery after system miniaturization. 14.8 mass% hydrogen equals an output of 2.94 kWh per kg sugar assuming an efficiency of PEM fuel cell of 50%, much higher than any current batteries (lead acid, ~0.030 kWh per kg; Ni–Cd, ~0.050 kWh per kg; Ni–MH, ~0.090 kWh per kg; Li ion, ~0.150 kWh per kg; and PL ion, ~0.150 kWh per kg).[9,10] High-energy density sugar can store more energy than batteries for transportation applications before refilling or recharging.[2] The real energy storage density of the sugar-battery will be lower than the theoretical value of 2.94 kWh per kg of sugar because of the volume and weight of the bioreformer, whose size will be decreased as technology improvements occur in the enzyme performance and PEM fuel cell configuration. The energy storage density will also depend on the weight ratio of fuel to the other parts. A critical advantage is that sugar fuels are supplied to the cell rather than being embedded with it.[73] For some special applications, such as air-independent-propulsion (AIP) submarines, the energy density of the sugar battery may be very close to its theoretical value (2.94 kWh per kg of fuel + fuel cell) because of the high ratio of fuel weight to the other components. The hypothetical super-high energy density sugar will be a very promising alternative compared to other developing batteries.[10]

As compared to current developing enzymatic biofuel cells,[10,73–75] the hypothetic sugar–hydrogen–PEM fuel cell systems have several advantages: (1) much higher energy extracting efficiency (122% *vs.* 15–20%), (2) several orders of magnitude higher energy output density (W m^{-2}), and (3) minimal product inhibition. Many attempts at enzymatic biofuel cells have been made recently to extract all the chemical energy in biofuels and convert it to electricity.[76,77] All sugar batteries must overcome the challenges, such as enzyme costs and enzyme stability.[74,78] For example, one kg of industrial immobilized thermostable glucose isomerase can convert at least 1 500 000 kg of glucose to fructose or have a turn-over number of ~800 000 000.[79,80] A startup company, Akermin, has claimed enzyme stabilization technology for three years by encasing enzymes in a proprietary, protective polymer structure. Another example is the more than one year shelf-life of glucose dehydrogenase at room temperature used in the blood sugar strips for diabetes patients. Obviously, the collaborations for enzyme and cofactor stabilization among groups of enzymatic biofuel cells, biosensors, and the hypothesized sugar-to-hydrogen–PEM fuel cell systems are expected.

4. Research and design perspectives

Before the above-mentioned applications are implemented, two major technical challenges must be overcome – (i) slow hydrogen production rate and (ii) high production cost.

Increasing the hydrogen production rate is the number one technological challenge because it is a requirement for all future applications. The proof-of-principle biohydrogen production experiment by the synthetic enzymatic pathway conducted by using off-the-shelf enzymes with some optimization has a reaction rate of 3.92 mmole of hydrogen per litre of reaction volume per hour.[60] The first significant improvement in reaction rates can be made by optimizing the enzyme ratio. We have estimated a potential improvement of at least ~20-fold by optimization of the rate-limiting step enzyme ratios and increasing substrate levels.[81] Second, another significant improvement will be implemented by increasing the reaction temperature. Currently, we are lacking thermostable enzymes. The rule of thumb suggests that most enzymatic reaction rates usually are doubled with every 10 °C increase (*i.e.*, Q_{10} effect). Therefore, an increase in the reaction temperature from 30 °C to 80 °C could result in another ~32 fold improvement. For example, the hyperthermophilic *P. furious* hydrogenase exhibits < 1% of its potential activity in the proof-of-principle experiment (32 °C). Increasing reaction temperature will decrease hydrogenase use and increase the overall reaction rate. Third, a 100-fold increase in enzyme concentration could lead another potential rate enhancement by 20–100 fold. Fourth, when the overall enzyme concentration is high, macromolecular crowding effects could lead to metabolite or substrate channeling between the cascade enzymes, which could contribute to another reaction rate enhancement by ~2–100 fold, which is observed sometimes, especially in macromolecular crowding conditions.[82–84] Finally, there will be a great enhancement potential in the turnover numbers for each enzyme by several orders of magnitude, because their catalytic efficiencies are still much lower than those catalytically perfect enzymes with a k_{cat}/K_m of 10^8–10^9 per M per s.[85,86] Based on the above analysis, an increase in hydrogen production rate by at least 3 orders of magnitude from the current levels will be reachable after intensive R&D efforts within several years. Comparatively, the power density of microbial fuel cells has been improved by greater than 10^4–10^6 fold during the past 10 years.[58,87]

To our knowledge, the highest biological hydrogen production rate is 11.8 moles of hydrogen per litre of reactor volume per hour, which is mainly implemented by using two combinatorial technologies: high enzyme loading and high substrate concentration.[71] This rate is high enough for some high power applications, for example, hydrogen–PEM fuel cell devices. Given the same reaction rate, a high-power vehicle equipped with a 100 kW (134 hp) PEM fuel cell stack would need an on-board

bioreformer having a reasonable volume of 210 litres, plus a peak battery with a several hundred kW electric motor.

High hydrogen production costs are associated with three key components – costly and unstable enzymes, the coenzyme ($NADP^+$), and the substrates. Decreasing the enzyme costs can be carried out by two main approaches – decreasing enzyme production costs and extending enzyme lifetime. The former can be mainly implemented by (a) producing recombinant enzymes rather than purifying them from natural biological entities,[88] (b) over-expressing the target enzymes,[88,89] (c) implementing high-cell density fermentation by using low-cost nutrients,[38] and (d) decreasing enzyme purification costs.[90–92] The latter (*i.e.*, stabilization of the enzymes) can be implemented by (a) immobilization on traditional materials or nano-materials,[93–99] (b) thermostable enzyme replacement,[100–103] (c) enzyme formulation,[104–106] and (d) enzyme engineering by directed evolution or rational design.[107–113] Recently, a hyperthermostable 6-phosphogluconate dehydrogenase (#4 enzyme) from the hyperthermophilic bacterium *Thermotoga maritima* has been over-expressed in *E. coli* with a yield of more than 200 mg per litre of culture. It is found to retain >90% of its activity at 80 °C for more than 48 hours (manuscript under preparation). Stabilization of one enzyme or multiple enzymes on solid supporters is a widely-known technology.[74,114] With the rapid development in nano-materials with much larger surface areas (*i.e.*, more enzymes can be immobilized), examples of ultra-stable immobilized enzymes have been reported to be active for one to several months.[93,96,98,115,116] It is expected that these combinatorial technologies will stabilize the enzymes for several months or even longer at ambient temperatures and at the evaluated temperature for more than 200 hours in the near future.

NAD(P) is not a stable under certain circumstances[117,118] but its stability can be enhanced greatly by chemical modifications or immobilization.[114,119] Asymmetric synthesis mediated by enzymes involving NAD(P)H regeneration is becoming more and more competitive in the pharmaceutical industry.[120,121] The reported total turnover number for cofactors is as high as 600 000[122] or even more than 1 million,[123] suggesting the economical feasibility of recycling NAD(P)H for hydrogen production.

Starch is food and animal feed, and its supply is becoming more restricted again. Cellulosic material is the most abundant renewable resource; the yearly energy production is ~6 fold of all human energy consumption.[124,125] If a small fraction of yearly cellulosic material (*e.g.*, 10%) is used for transportation, transportation fuel independence will be reached. Cellulose has the same chemical formula as starch except with different glucosidic bond linkage between anhydroglucose units.[61] Producing hydrogen from cellulosic materials must overcome two obstacles: (1) increasing cellulose reactivity for fast reaction rates and (2) discovery or development of cellulose phoshorylases that can phosphorolyze β-1,4-glucosidic bonds. With regard to obstacle 1, the crystalline cellulose structure can be completely broken by using cellulose solvents, such as concentrated phosphoric acid,[126–128] ionic liquids[129–131] and so on. The presence of lignin and hemicellulose in natural lignocellulose negatively influences cellulose hydrolysis rates and digestibility. The best lignocellulose pretreatment will be implemented if (1) hemicellulose and lignin can be removed efficiently, (2) crystalline cellulose can be converted to amorphous cellulose, (3) low processing costs are attained, and (4) low capital investment is used. Recently, a new cellulose solvent- and organic solvent-based lignocellulose fractionation (COSLIF) technology that combines a cellulose solvent (concentrated phosphoric acid) and a organic solvent featuring modest reaction conditions (*e.g.*, 50 °C and atmospheric pressure) aims at lignin, hemicellulose, and cellulose at the same time.[128,132] Very high cellulose digestibilities (~97%) by cellulase are obtained for a number of feedstocks (*e.g.*, corn stover, switchgrass and hybrid poplar) within a short hydrolysis time of 24 hours. With regard to obstacle 2, cellobiose and cellodextrin phoshosphorylases[63,69,133–135] may be the starting enzymes for creating unnatural or undiscovered cellulose phosphorylase.

Costs of hydrogen production from carbohydates (*e.g.*, \$0.18 per kg of carbohydrate) would be as low as ~\$2 per kg of H_2, assuming that feedstock costs account for 60% of overall costs and enzymes and co-enzymes account for 40%. In general, approximately 40–75% of commodity prices, such as gasoline from crude oil, hydrogen from natural gas, and ethanol from corn kernels, come from feedstock costs.[136] If the enzymes were produced as cheaply as industrial enzymes (*e.g.*, cellulase, amylase, protease), and their stability was enhanced to the same level of immobilized glucose isomerase,[80] the estimated hydrogen production costs through this enzymatic biocatalysis would be far lower than \$2 per kg of hydrogen.

An alternative way to decrease the costs of enzymes and coenzyme for hydrogen production is to put the synthetic enzymatic pathway containing 13 over-expressed enzymes into a minimal bacterium[137] or create a new super hydrogen production microorganism by total synthesis of the whole genomic sequence.[138] But the implementation of the hypothesized new bacteria will take a long time, the hydrogen yields must be a little lower than 12 H_2 per glucose unit due to cellular biomass synthesis, and the hydrogen production rates could be very slow for some applications due to membrane blockage.[67,139]

To implement sugar-powered cars, a number of process engineering challenges have to be overcome, for example, warm-up of the bioreformer, shut-down of the bioreformer, temperature controlling for the coupled bioreformer and fuel cells, mixing and gas release control for the bioreformer, and re-generation of used enzymes and co-enzymes in the bioreformer, to name a few. But such technical challenges can be solved if the great potential is widely realized.

5. Conclusion

Hydrogen production by synthetic enzymatic pathways is the most efficient way to convert the energy stored in renewable sugars to hydrogen energy.[26,60] In addition, an endothermic reaction at ambient temperature means absorption of some low-temperature heat energy and conversion to a high-quality chemical energy carrier – hydrogen.[26,60,67] Hydrogen production from the enriched chemical energy source – sugars produced from photosynthesis – suggests minimal challenges for scale-up and storage of feedstocks. We now need to address both increasing the hydrogen production rates and decreasing the hydrogen production costs. With technological improvements, this carbohydrate-to-hydrogen technology will address the

challenges associated with hydrogen production, storage, safety, distribution, and infrastructure in the hydrogen economy.[26]

We envision that we will drive sugar-powered vehicles having a driving distance of >300 miles per refill. Solid sugar (~27–68 kg of sugars or 4–10 kg of hydrogen per refilling) will be added at local outlets such as grocery stores and the like. The on-board bioreformer with a volume of several tens or hundreds of litres containing a number of stabilized enzyme cocktails will convert sugar syrup to hydrogen, which will be converted to electricity quickly with very high energy efficiency and high power density *via* the PEM fuel cell. As a result, driving tomorrow with renewable sugars will no longer be viewed as science fiction! These systems will be the most energy efficient and greenest power-train with high power density and high energy storage density. This ambitious project of the sugar-powered vehicle will become a hen that will lay golden eggs for various sub-directions – enzyme engineering, enzyme immobilization, synthetic biology, fuel cells, battery, powertrain system integration, and so on.

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Energy Efficiency Analysis: Biomass-to-Wheel Efficiency Related with Biofuels Production, Fuel Distribution, and Powertrain Systems

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Abstract

Background: Energy efficiency analysis for different biomass-utilization scenarios would help make more informed decisions for developing future biomass-based transportation systems. Diverse biofuels produced from biomass include cellulosic ethanol, butanol, fatty acid ethyl esters, methane, hydrogen, methanol, dimethyether, Fischer-Tropsch diesel, and bioelectricity; the respective powertrain systems include internal combustion engine (ICE) vehicles, hybrid electric vehicles based on gasoline or diesel ICEs, hydrogen fuel cell vehicles, sugar fuel cell vehicles (SFCV), and battery electric vehicles (BEV).

Methodology/Principal Findings: We conducted a simple, straightforward, and transparent biomass-to-wheel (BTW) analysis including three separate conversion elements -- biomass-to-fuel conversion, fuel transport and distribution, and respective powertrain systems. BTW efficiency is a ratio of the kinetic energy of an automobile's wheels to the chemical energy of delivered biomass just before entering biorefineries. Up to 13 scenarios were analyzed and compared to a base line case – corn ethanol/ICE. This analysis suggests that BEV, whose electricity is generated from stationary fuel cells, and SFCV, based on a hydrogen fuel cell vehicle with an on-board sugar-to-hydrogen bioreformer, would have the highest BTW efficiencies, nearly four times that of ethanol-ICE.

Significance: In the long term, a small fraction of the annual US biomass (e.g., 7.1%, or 700 million tons of biomass) would be sufficient to meet 100% of light-duty passenger vehicle fuel needs (i.e., 150 billion gallons of gasoline/ethanol per year), through up to four-fold enhanced BTW efficiencies by using SFCV or BEV. SFCV would have several advantages over BEV: much higher energy storage densities, faster refilling rates, better safety, and less environmental burdens.

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Introduction

The sustainability revolution from non-renewable sources to renewable sources is the defining challenge of our time [1,2,3]. Mobility usually represents the level of a civilization [4,5]. Light-duty passenger vehicles, which constitute the largest type of transportation energy consumption among different transportation modes, have some special requirements, such as high energy storage capacity in a small container (e.g., ~50 liters), high power output (e.g., ~20–100 kW per vehicle), affordable fuel (e.g., $~20–30/GJ), affordable vehicle, low costs for rebuilding the relevant infrastructure, fast charging or refilling of the fuel (e.g. several min per time), and safety concerns [5,6,7]. Such strict requirements result in limited choices for fuels and respective powertrain systems. Here powertrain refers to the group of components that generate power from stored energy and deliver it to wheels of vehicles running on the road surface, including the engine, transmission, drive shaft, differentials, and wheels [8,9]. Therefore, current light-duty passenger vehicles mainly rely on non-renewable liquid fuels and internal combustion engines (ICE). But the depletion of crude oil, accumulation of greenhouse gases, concerns of national energy security, and creation of manufacturing jobs are motivating the development of sustainable transportation biofuels based on local renewable biomass [1,3,9,10].

Most ethanol is made from corn kernels and sugarcane, but this practice raises heated debate due to competition with food supplies; furthermore, its contribution to the transport sector is minimal or modest [1,11]. Lignocellulosic biomass is presently believed to be the only major renewable bioresource that can produce a significant fraction of liquid transportation fuels and renewable materials in the future [2,9,11,12] because the overall energy stored in phytobiomass each year is approximately 30-fold of the energy consumed for transportation [9,13]. But the future role of biomass in the transport sector remains in debate [1,14,15].

A great variety of biofuels can be produced from lignocellulose biomass, including cellulosic ethanol [10,16], butanol and/or long chain alcohols [17,18], electricity [19,20], bioalkanes [21], fatty acid esters [6,22,23], hydrogen [24,25,26,27], hydrocarbons [28, 29], and waxes [22]. The biofuels that will become short-, middle- and long-term transportation fuels is a matter of vigorous debate. Among them, some biofuels may have a particular niche market. For example, jet planes require high-density liquid fuels [6,17, 21,22]. First, the analysis presented here is restricted to the largest transportation fuel market – fuels for light-duty passenger vehicles. Second, this analysis starts from less costly lignocellulosic biomass that can be collected and delivered at reasonable costs (e.g., ~$60–100 dollars per ton) [9,11]. Third, algal biofuel production or other renewable electricity generation (e.g., solar and wind electricity) is not covered in this paper.

Several types of powertrain systems have been developed to convert stored energy to kinetic energy, including internal combustion engines (e.g., gas ICE, diesel ICE, jet turbine, and rocket turbine), external combustion engines (e.g., steam engine and steam turbine), and electric motors. Because of special requirements of passenger vehicles, such as weight-to-power ratio (e.g., one to several g/W), engine costs (e.g., tens dollars/kW), and engine lifetime (e.g., ~5,000 h), only three engines are acceptable for passenger vehicles: gas ICE, diesel ICE, and electric motor. Considering electricity stored in batteries and possible on-board electricity generation systems (e.g., hydrogen proton exchange membrane (PEM) fuel cell) plus their hybrids, this analysis attempted to compare six current and future powertrain systems: gas-based ICE vehicles (ICE-gas) [7,8], hybrid electric vehicles based on gasoline ICE (HEV-gas) [30], hybrid electric vehicles based on diesel (HEV-diesel) [30], fuel cell vehicles based on compressed H_2 (FCV) [31,32,33,34], battery electric vehicles (BEV) [20,32], and sugar (hydrogen) fuel cell vehicles (SFCV) [3,5,9].

Numerous life cycle analyses (LCA) have been conducted to investigate the potential impacts of biomass/biofuels on energy applications, greenhouse gas emissions, and even water footprint [10,14,15,35,36,37,38,39,40,41,42,43,44]. But such analyses rely heavily on numerous assumptions, uncertain inputs (e.g., fertilizers, pesticides, farm machinery), energy conversion coefficients among different energy forms and sources, system boundaries, and so on. For example, conflicting conclusions have been made even for well-known corn ethanol biorefineries [10,36,37].

Here we suggest developing an energy efficiency analysis for biomass-to-wheel (BTW), a ratio of kinetic energy of the wheels of an automobile to the chemical energy of delivered biomass (Fig. 1). Conducting this BTW analysis is simple and straightforward because it not only avoids uncertainties or debates for (i) biomass production-related issues, (ii) feedstock collection and transport, and (iii) land use change, but also excludes water consumption issues and greenhouse gas emissions in the whole biosystem. Therefore, energy efficiency analysis (but not life cycle analysis) may not only be helpful in narrowing down numerous choices before more complicated LCA and techno-economic analyses are conducted, but may also increase the transparency of such analyses.

In this article, we present a simple biomass-to-wheel (BTW) efficiency (η_{BTW}) analysis methodology involving three elements -- biomass-to-fuel (BTF), fuel distribution, and fuel-to-wheel (FTW) (Fig. 2). Using this method, 13 combinations of different biomass-to-biofuel approaches and their respective powertrain systems were analyzed as compared to a baseline – corn-ethanol-ICE. The identification of high BTW efficiency scenarios would help make a more informed decision for how to utilize (limited) biomass resource more efficiently. Following this, a more detailed LCA should be conducted for evaluating potential impacts associated with identified inputs and releases and for compiling an inventory of more relevant energy and material inputs as well as environmental effects.

Methods

The biomass-to-wheel efficiency (η_{BTW}), an energy conversion ratio of an automobile's kinetic energy to the harvested and delivered biomass in the front of the door of biorefineries, involves three sequential elements – biomass-to-fuel production, fuel transport and distribution, and the powertrain system responsible for the fuel-to-wheel conversion (Fig. 2). The BTW efficiency is the lumped efficiency from chemical energy in biomass to kinetic energy for vehicle driving. The η_{BTW} value can be calculated as below

$$\eta_{BTW} = \frac{W}{E_B} = \eta_{BTF} * (1 - \eta_{TDL}) * \eta_{FTW} \quad (1)$$

where

W is the kinetic energy transferred to wheels;

E_B is the chemical combustion energy of the biomass, where dry corn stover as a typical biomass contains ~65% carbohydrates (cellulose and hemicellulose, mainly), ~18% lignin, ~5% ash, ~12% other organic molecules [45,46]; and the E_B value is 16.5 MJ of low heating value/kg of corn stover [47];

η_{BTF} is the biomass-to-fuel (BTF) efficiency through biorefineries or power stations without significant inputs or outputs of other energy;

η_{TDL} is the fuel loss efficiency during its transport and distribution; and

η_{FTW} is the fuel-to-wheel (FTW) efficiency from the fuel to kinetic energy through powertrain.

The η_{BTF} value can be calculated as below

$$\eta_{BTF} = E_F / E_B \quad (2)$$

where E_F is the fuel produced in biorefineries or power stations. The η_{BTF} values of current corn ethanol as a reference range from 46% to 50% [48], and the value of 49% is chosen as a baseline [10]. Through the biomass sugars platform, potential biofuels include cellulosic ethanol, butanol, fatty acid esters (ester-diesel), hydrogen, and methane. Through syngas made by a thermochemical pathway, potential biofuels are ethanol, hydrogen, methanol, dimethyl ether (DME), FT-diesel, and electricity [49,50,51]. Also, electricity can be produced through direct combustion for the generation of steam followed by a steam turbine/generator, or biomass integrated gasification combined cycle (BIGCC) to fuel cells (Table 1).

Different powertrains are required to convert different biofuels to the kinetic energy of the wheels. The η_{FTW} value can be calculated as a ratio between the kinetic energy on wheels (W) and fuel energy in the tank (E_T):

$$\eta_{BTW} = W / E_T \quad (3)$$

For liquid biofuels, powertrain systems are gasoline ICE, HEV-gas, and HEV-diesel. Fuel cell vehicles run on stored compressed hydrogen, through a PEM fuel cell stack and an electric motor. The sugar fuel cell vehicle (SFCV) is a hypothetical powertrain system, where sugar is a hydrogen carrier, an on-board biore-

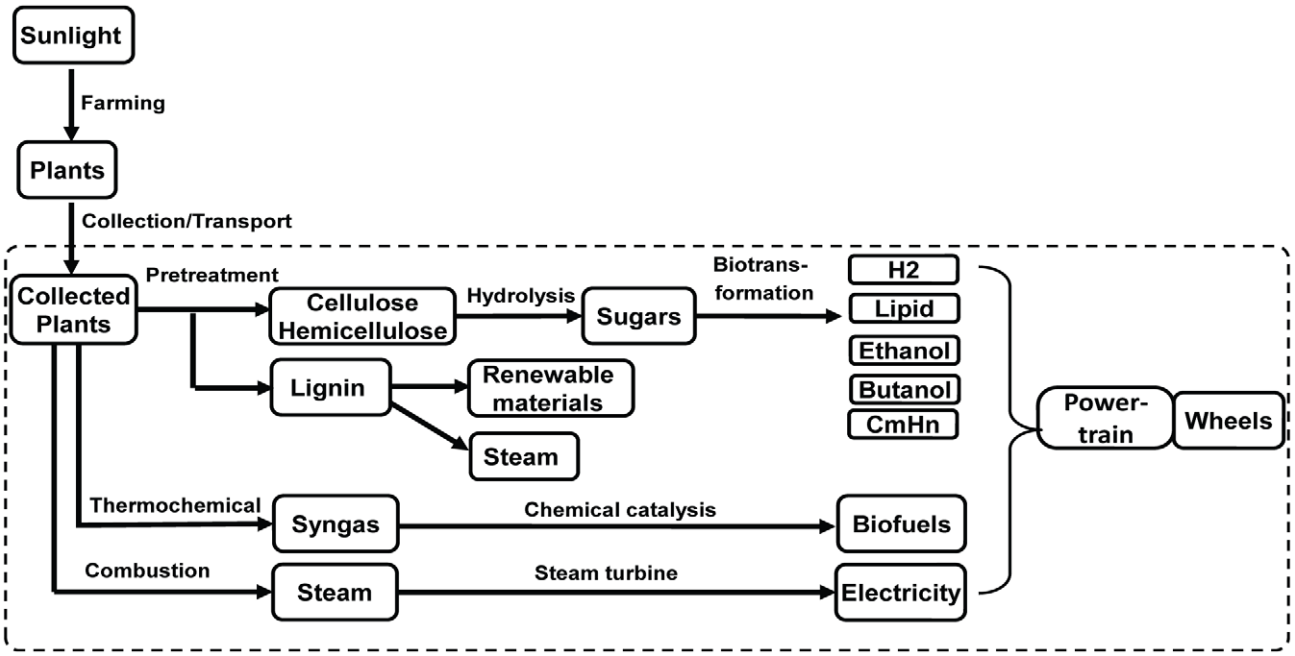

Figure 1. Different pathways for biofuels production from lignocellulosic biomass. The current energy efficiency analysis focuses on the delivered biomass-to-wheel efficiency related with conversion, transportation and power train systems.
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former generates high-purity hydrogen for PEM fuel cell stacks, and the remaining powertrain parts are the same as FCV [5,9]. The battery electricity vehicle (BEV) is a battery/motor system based on rechargeable batteries that can store electricity.

The η_{TDL} value can be calculated as fuel consumed for its transport and distribution from biorefineries to end-users (vehicles)

$$\eta_{TDL} = E_C/(E_C + E_T) \quad (4)$$

where E_C is the energy consumed in the process of fuel transport and distribution, E_T is the fuel energy delivered to end users (i.e., powertrains), and $E_F = E_C + E_T$.

Fuel losses during transport and distribution were obtained from the Argonne National Laboratory's model Greet 1.8c [52]. Detailed data sources and efficiency calculations are available in Table 2.

Results

Different scenarios of fuel production through sugar, syngas, and steam platforms as well as six different powertrains viz. internal combustion engine vehicle (ICE), hybrid electric vehicle-gas (HEV-gas), hybrid electric vehicle-diesel (HEV-diesel), (hydrogen) fuel cell vehicle (FCV), battery electric vehicle (BEV), and sugar fuel cell vehicle (SFCV) are shown in Figure 3.

Biomass-to-fuel efficiency (η_{BTF})

All biomass-to-fuel efficiency data plus their original data and units for different biomass pathways are listed in Table 1, and their representative η_{BTF} values are presented in Fig. 4.

In this study, we use corn stover as a representative biomass, in which total carbohydrates (including cellulose and hemicellulose) account for approximately 60–65% of combustion energy in biomass. Through the biochemical (sugar) pathway, the remaining chemical energy in biomass, mainly lignin, is consumed for running pretreatment as well as sugar isolation and product separation [45]. In general, ~35–40% of the chemical energy of biomass is enough to run biorefineries without external energy input [45,53]. The η_{BTF} values for sugar-to-biofuels mainly depend on sugar isolation yields and sugar-to-fuel yields during microbial fermentation or enzymatic biotransformation. In this study, the η_{BTF} value is 57%, i.e., ~88–95% of sugar release from

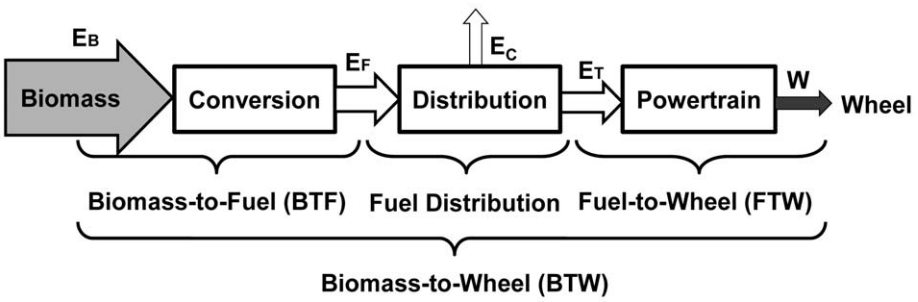

Figure 2. The scheme of energy efficiency analysis for biomass-to-wheel efficiency calculation -- $\eta_{BTW} = \frac{W}{E_B} = \eta_{BTF} * (1 - \eta_{DL}) * \eta_{FTW}$.
doi:10.1371/journal.pone.0022113.g002

Table 1. Biomass-to-fuel (BTF) efficiency through different biomass utilization pathways.

Biofuel	Technology	Feedstock	Efficiency	Original Data	Original Data unit	Reference
corn ethanol	fermentation	corn	46.4%	0.372	L/kg dry	[95]
	fermentation	corn	49.4%	0.396	L/kg dry	[10]
	fermentation	corn	50.1%	0.402	L/kg dry	[48]
cellulosic ethanol	fermentation	corn stover	48.4%	0.298	kg/kg	[45]
	fermentation	corn stover	55.6%	0.342	kg/kg	[53]
sugar	hydrolysis	corn stover	55.8%	0.652	kg/kg	[53]
	hydrolysis	corn stover	61.1%	0.714	kg/kg	[58]
hydrogen	gasification	wood	55.0%	55.00	%LHV	[57]
	gasification	almond shells	70.8%	74%	HHV	[58]
methanol	gasification	wood	50.9%	0.477	kg/kg	[59]
	gasification	lignocellulose	54.9%	59.0	%HHV	[58]
DME	gasification	energy crop	39.0%	39–56.8%	LHV	[60]
FT-diesel	gasification	lignocellulose	41.4%	42.0	%HHV	[31]
	gasification	lignocellulose	52.0%	52.0	%LHV	[61]
ester micro-diesel	fermentation	glucose	7.2%	14.0	% theoretical efficiency	[22]
	fermentation	glucose	36.5%	64	%LHV	[6]
butanol	fermentation	glucose	46.7%	0.350	g/g glucose	[17]
	fermentation	glucose	52.8%	92.6%	LHV	[6]
methane	fermentation	ley crops	62.2%	10.6	GJ/dry ton	[54]
	fermentation	energy maize	81.3%	0.374	m^3/kg dry maize	[55]
electricity	boiler	lignocellulose	25–43%	25–43%	LHV	[62]
electricity	BIGCC	lignocellulose	45.0%	45.0%	LHV	[63]
	BIGCC	lignocellulose	32–40%	32–40%	LHV	[62]
electricity	molten carbonate FC	lignocellulose	40.2%	40.2%	LHV	[64]
electricity	FC	lignocellulose	51.0%	51.0%	LHV	[65]

doi:10.1371/journal.pone.0022113.t001

biomass, in agreement with data elsewhere [45]. Given sugar yields of 88–99% for cellulose and hemicellulose and sugar-to-ethanol yields of 92–95%, the η_{BTF} value of cellulosic ethanol would be 50%, with a range of 48–56% [10,53]. Given the sugar-to-butanol yields from 82% (now) [17] to 93% (future) [6], the η_{BTF} value for butanol fermentation would be about 48% with a range of 47–53%. Methane can be produced by anaerobic fermentation mediated by a microbial consortium, where micro-organisms convert all organic components except non-hydrolytic lignin to methane. Therefore, η_{BTF} values range from 62 to 81% [54,55]. The practical η_{BTF} value of methane may be approximately 65%, higher than 50% (ethanol) and 48% (butanol). In contrast to anaerobic biofuels fermentations, long chain fatty acid esters (microdiesel) must be produced from sugars through semi-aerobic fermentation due to an imbalance of NAD(P)H [6,22,23]. Because semi-aerobic fermentation consumes a significant amount of sugar for the synthesis of cell mass than anaerobic fermentation, less carbohydrate would be allocated to the production of micro-diesel [6,56]. The η_{BTF} values of the ester-diesel fermentation would be about 35%, in the range of 7 to 37% depending on the fuel yields, from 13% [22] to 64% (future) [6].

Table 2. Distribution energy efficiency loss*.

Distribution energy efficiency loss		Input data (Greet 1.8c *)	
Biofuel	**Efficiency loss %**	**Energy input**	**Unit**
Electricity	8.00	8.00	%
FT-diesel	1.53	15,557	btu/mmbtu
Dimethylester	3.10	31,980	btu/mmbtu
Methanol	3.29	34,021	btu/mmbtu
Hydrogen	17.5	211,654	btu/mmbtu
Methane	7.54	81,550	btu/mmbtu
Sugar	1.47	5,979	btu/bushel
ester-diesel	0.75	7,541	btu/mmbtu
Butanol	1.35	13,636	btu/mmbtu
Ethanol	1.71	17,387	btu/mmbtu

*http://www.transportation.anl.gov/modeling_simulation/GREET/index.html.

doi:10.1371/journal.pone.0022113.t002

Syngas can be produced from biomass through gasification – partial combustion at temperatures above 1000 K and in the presence of oxygen and/or water. Gasification is a relatively mature technology, so a significant fraction of biomass must be consumed for partial combustion, resulting in relatively low energy efficiencies, even though all organic components can be utilized [49,50,51]. The η_{BTF} values for hydrogen generation from biomass range from 55% [57] to 71% [58] with a mean value of ~60%. The η_{BTF} values for methanol, DME and FT-diesel vary from 51% [59] to 55% [31], from 39% to 57% [60], and from 41% [31] to 52% [61], respectively. Preferred η_{BTF} values

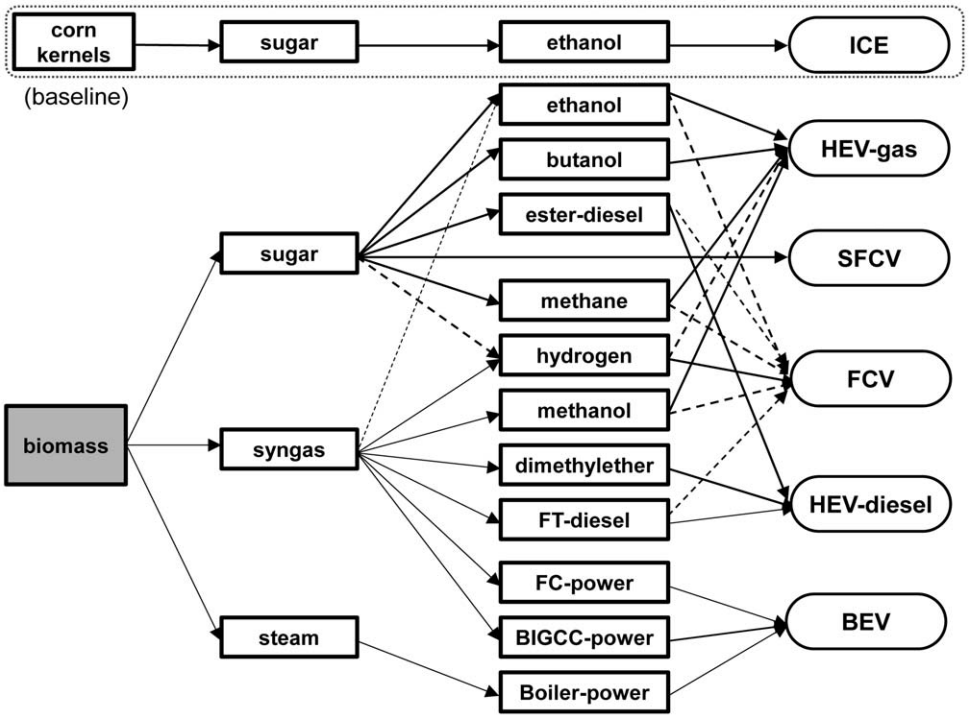

Figure 3. Scenarios of the production of fuels from biomass and their respective fuel power train systems. Solid lines represent the scenarios that we analyzed; the dotted lines represent possible scenarios that we did not analyze.
doi:10.1371/journal.pone.0022113.g003

are 54% (methanol), 52% (DME), and 51% (FT-diesel), respectively. Clearly, the η_{BTF} values for liquid biofuels (methanol, DME and FT-diesel) are lower than those of hydrogen because of more catalysis steps and their accompanied energy losses.

Bioelectricity can be produced simply through boiler/steam turbine technology, with η_{BTF} values ranging from 25% (now) to 43% (future) [62]. The assumed η_{BTF} value is approximately 32%. Biomass integrated gasification, combining gas and steam turbine for electricity production (BIGCC), would have improved overall efficiencies, ranging from 32 to 45% [62,63]. In order to increase electricity generation efficiency without restriction of the second law of thermodynamics for turbines, the integrated biomass gasification and fuel cells would have η_{BTF} values of 40 to 51% [64,65].

Transport and distribution loss efficiency (η_{TDL})

Fuel distribution processes consume a fraction of fuel produced from biorefineries or power stations (Fig. 5). Original data and units were obtained from the Greet1.8c software (Table 2). Typical η_{TDL} values for different fuels after normalization are shown in Figure 5. In general, liquid biofuels have similar efficiency losses (e.g., 0.8–3.3%). Gaseous fuels, such as hydrogen and methane, have more energy consumption for their compression, transport, refilling, and so on. The η_{TDL} values are 17% for compressed

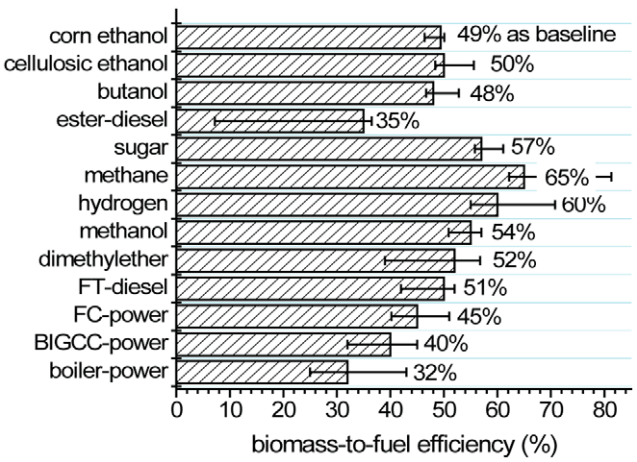

Figure 4. Comparison of biomass-to-fuel (BTF) efficiency in the biorefineries or power stations.
doi:10.1371/journal.pone.0022113.g004

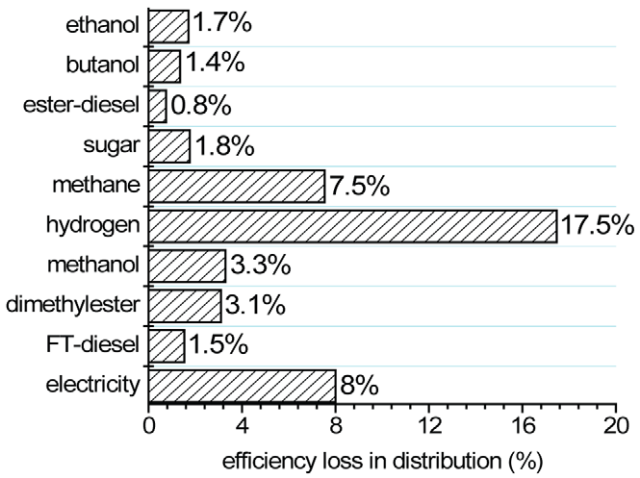

Figure 5. Comparison of transport and distribution loss efficiency for different fuels.
doi:10.1371/journal.pone.0022113.g005

hydrogen and 8% for compressed methane (Greet1.8c). The well-documented distribution efficiency of electricity is 92%, i.e., 8% of electricity is lost during its distribution (Greet1.8c).

Fuel-to-wheel efficiency (η_{FTW})

Two major internal combustion engines for passenger vehicles are gasoline Otto (spark plug firing) ICE and diesel (compression ignition) ICE. Gasoline ICEs have a low weight-to-power ratio (e.g., ~1 g engine per W output) but their maximum efficiencies are relatively low, approximately 32%, due to low compression ratios [66]. In contrast, diesel ICEs have a higher weight-to-power ratio (e.g., ~3–4 g engine per W output) and a much higher energy conversion efficiency, more than 40% [66]. It is reasonable that diesel ICEs are widely used in heavy-duty trucks, tanks, and tractors. In Europe, diesel ICE passenger vehicles are more popular mainly due to higher fuel costs and more climate change concerns. Audi A3 vehicles based on ICE-diesel have 35.4 miles per gallon of diesel, higher than ICE-gasoline (24.7 miles per gallon of gasoline) [67], suggesting a ~26% enhancement in η_{FTW} efficiency. (Note: the volumetric energy density of diesel is ~13–14% higher than that of gasoline) [7].

Practical η_{FTW} values of ICEs are much lower than their maximum efficiency because of (i) the engines operate at ~70% of their maximum efficiency during most driving conditions, (ii) ~17% loss for engine idling, (iii) ~2% consumption for accessories (e.g., air conditioning, lighting), and (iv) ~25% loss in transmission [30,66,68]. Therefore, the η_{FTW} for ethanol-ICE is approximately 14% as a baseline [69], and this value would be improved through higher compression rate ethanol engine and better transmission [70,71,72]. Advanced diesel vehicles are expected to have η_{FTW} values of 20–24% [71]; the η_{FTW} value of 23% is used in this study.

Hybrid electric vehicles (HEV) can eliminate idling losses, allow a small engine to work at nearly optimal conditions, and utilize braking energy with regenerative braking [30,73]. Therefore, advanced HEV-gas is estimated to have η_{FTW} values of 29–34% [30,74]. Similarly, the η_{FTW} values of HEV-diesel can be increased to 32–38%, with a preferred value of 37%.

The hydrogen fuel cell vehicle (FCV) is a complicated powertrain system involving compressed hydrogen, FEM fuel cells, an electric motor, and a rechargeable battery [32,75]. FCVs feature zero tailpipe pollution and high energy conversion efficiencies due to PEM fuel cells, whose theoretical energy efficiency from hydrogen to electricity is up to 83%. As a result, many companies have attempted big research FCV projects, and some of them produced prototype FCVs, such as the GM Sequel, the BMW Hydrogen 7, the Ford Focus FCV-Fuel Cell, the Toyota Fine X, and the Honda FCX Clarity. The η_{FTW} values of FCVs range from 41 to 54% [32,75], with a mean value of 45%. SFCVs based on FCVs would have an on-board bioreformer that can convert the sugar slurry to high-purity hydrogen and absorb waste heat from PEM fuel cells. Because the efficiency of sugar-to-hydrogen is 107% based on low heating value [9,24,25], the η_{FTW} value for SFCV is estimated to be 48% with a range of 44–57%.

Battery electric vehicles (BEV) have the highest η_{FTW}values, although they still have some energy losses in battery recharging and release, storage loss, motor, and so on [32,76]. BEVs have predicted η_{FTW} values from 64 to 86% [32,76,77], with a mean value of 68%. All fuel-to-wheel efficiencies of different vehicles are summed up in Table 3 and Fig. 6.

Biomass-to-Wheel (BTW) efficiency (η_{BTW})

A combination of 12 kinds of biofuel production approaches and 6 kinds of advanced powertrains for passenger vehicles results in more than 20 scenarios (Fig. 3). In this analysis, 14 scenarios were calculated (Fig. 7). The current corn ethanol/ICE scenario has η_{BTW} value of ~7%, i.e., only 7% of the chemical energy in corn kernels is converted to the kinetic energy on wheels, implying a great potential in increasing biomass utilization efficiency. An ethanol HEV-gas system would double η_{BTW} values to 14–18%, suggesting the importance of developing hybrid electric vehicles based on available liquid fuel distribution system. There is no significant difference in η_{BTW} between butanol and ethanol, but butanol may have other important future applications, such as powering jet planes. The η_{BTW} values of methane/HEV-gas and methanol/HEV-gas are 19% and 17%, respectively, higher than those of ethanol and butanol, mainly due to higher product yields. Since ICE-diesel has higher η_{FTW} efficiencies than ICE-gas, the scenarios based on HEV-diesel through DME and FT-diesel (except ester-diesel) would have higher η_{BTW} values than HEV-gas scenarios. For ester-diesel, a significant amount of energy is lost during aerobic fermentation due to thermodynamic and bioenergetic limits [6], resulting in low η_{BTW} values. Even for the niche jet fuels market, the production of ester-diesel through semi-aerobic microbial fermentation might not be competitive with anaerobic butanol fermentation [78] and a high-energy-retaining efficiency hybrid of biocatalysis and chemical catalysis [28].

Although (hydrogen) fuel cell vehicles (FCVs) have higher η_{FTW} efficiencies than ICE-gas and ICE-diesel, the H_2/FCV scenario

Table 3. Fuel-to-wheel (FTW) efficiency for different powertrains.

Powertrain	Efficiency	Reference
ICE-gas	11.3–15.2%	[30,69,70,71]
ICE-diesel	20–24%	[71]
HEV-gas	28.8–31.4%	[30,74]
HEV-diesel	34.6–37.6%	based on HEV-gas [30,74] and ICE-diesel [71]
FCV	41.0–53.8%	[32,75]
SFCV	43.7–57.3%	based on FCV plus sugar to H_2 biotransforming efficiency [6,24,25]
BEV	64.4–86%	[32,76,77]

doi:10.1371/journal.pone.0022113.t003

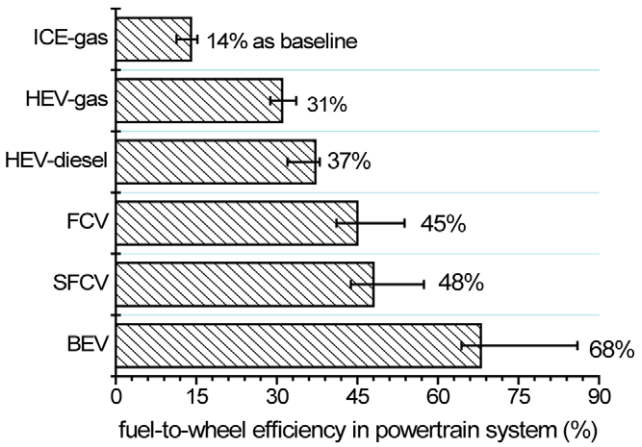

Figure 6. Comparison of fuel-to-wheel (FTW) efficiency for different powertrain systems.
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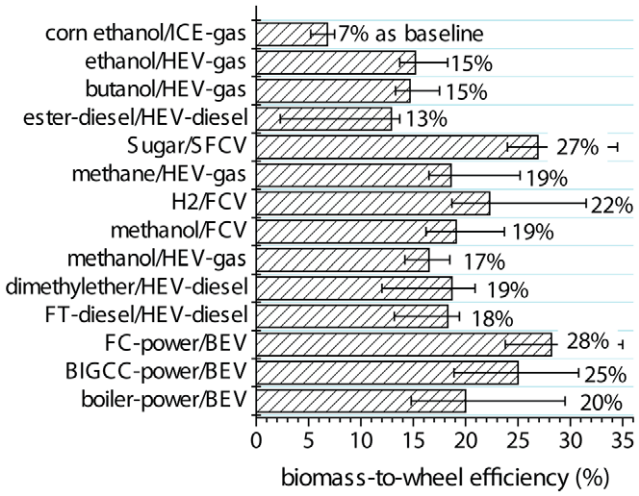

Figure 7. Comparison of biomass-to-wheel (BTW) efficiency for different biomass utilization scenarios.
doi:10.1371/journal.pone.0022113.g007

shows ~46% and ~15% η_{BTW} enhancements over ethanol HEV-gas and DME HEV-diesel, respectively, because significant energy loss in hydrogen distribution discounts FCV's advantages over HEV-diesel. The sugar/SFCV scenario would have very high η_{BTW} values of approximately 27% due to lower energy consumption in fuel transport and heat recapture in the sugar-to-hydrogen biotransformation, compared to the H_2/FCV scenario.

BEV scenarios are among the highest η_{BTW} values, from 20% to 28%, with increasing electricity generation efficiencies from direct combustion, BIGCC, to FC-power.

Discussion

Conducting energy efficiency analysis is simpler, faster, and less controversial than conducting life cycle analysis because the latter heavily depends on so many different assumptions and uncertain inputs. Here we present a straightforward energy efficiency analysis from biomass to wheels for different options, which contains three elements. Each element can be analyzed separately and adjusted individually; most of which have data well-documented in literature (Tables 1–3). Because of the same input and output in all cases, an increase in energy conversion efficiency nearly equals impact reductions in carbon and water footprints on the environment. Most of the results obtained from this biomass-to-wheel analysis were in good agreement with previous, more complicated life cycle analyses, supporting the validity of this methodology. Our analysis suggested that the hydrogen fuel cell vehicle (H_2/FCV) scenario would have at least comparable efficiency with or a little higher than hybrid electric vehicle (HEV) systems, which was supported by a previous paper [76]. Another analysis suggested that the H_2/fuel cell scenario had three times higher efficiency than ethanol/internal combustion engines (ICE) [33], in good agreement with our analysis (Fig. 7). Through comparison of four biofuels (i.e., hydrogen, methanol, Fischer–Tropsch (FT)-diesel, and ethanol) and two powertrain systems (i.e., ICE and FCV), they recommended FCV due to the highest energy efficiency [31]. These data were comparable with our analysis (Fig. 7). Both the sugar/sugar fuel cell vehicle (SFCV) and fuel cell (FC)-power/battery electric vehicle (BEV) scenarios would have nearly four times that of corn ethanol/ICE-gas, implying the importance of enhancing BTW efficiency in each conversion element.

A new solution -- sugar-fuel cell vehicles (SFCV)

The concept of SFCV was proposed to address problems associated with H_2/FCV, such as high-density hydrogen storage in FCV, low-cost sustainable hydrogen production, costly hydrogen distribution infrastructure, and safety concern [9,25]. In this system, renewable sugar (carbohydrate) is suggested as a high hydrogen density carrier, with a gravimetric density of 8.33% mass H_2 and a volumetric density of more than 100 g H_2 per liter [3,5,9]. Transportation and distribution of the sugar/water slurry or sugar slurry would be easily achieved using available infrastructure. This hypothetical SFCV based on FCV would contain a sugar tank and an on-board sugar-to-hydrogen bioreformer, with a combined sugar tank and bioreformer volume that is much smaller than a compressed hydrogen tank or other hydrogen storage approaches [3,5]. The sugar/water slurry would be refilled rapidly into the sugar container in SFCVs at local sugar stations; the on-board biotransformer would convert the sugar solution to high-purity hydrogen and carbon dioxide using a stabilized enzyme cocktail; and a small-size hydrogen storage container would serve as a buffer, balancing hydrogen production and consumption. In addition, feeding a mixture of CO_2/H_2 or pure hydrogen in the proton exchange membrane (PEM) fuel cells would dramatically decrease system complexity and greatly increase system operation performance, and the waste heat release from PEM fuel cells would be coupled to the heat needed by the bioreformer. Electrical energy from PEM fuel cells would be sent to the motor controller/motor/gears to generate kinetic energy [9]. When extra kinetic energy is needed for acceleration or start-up, electrical energy stored in the rechargeable battery would be released, like in a hybrid electric vehicle [9]. The on-board bioreformer in SFCVs, mediated by the thermoenzyme cocktails under modest reaction conditions (e.g., ~80°C and ~1 atm), may be capable of providing high-purity hydrogen at a rate of ~23.5 g H_2/L/h or higher. Given a bioreformer size of 42.8 L, one kg of hydrogen per hour could then be produced to drive the PEM fuel cell stack, followed by the electric motor [5]. High-speed biohydrogen production rates have been implemented by high cell-density microbial fermentation [79]. It is widely known that enzymatic reactions usually are at least one order-of-magnitude faster than microbial fermentations because the former has no cellular membrane to slow down mass transfer and much higher biocatalyst loadings, without the dilution of other biomacromolecules (e.g., DNA, RNA, other cellular proteins) [3,56,80,81]. Current gasoline/ICE cars require maintenance every 3,000 miles (e.g., 4,800 km) or 3 months, i.e., 50–100 driving hours. Discovery of thermophilic enzymes that are stable at ~80°C for more than 100 h has been demonstrated, for example, *T. maritima* 6-phosphogluconate dehydrogenase [82]. We expect that enzyme deactivation in the biotransformer will be solved through infrequent service maintenance, similar to the oil/air filter change for gasoline/ICE vehicles. Several technical obstacles of SFCVs include poor enzyme stability, labile and costly coenzymes, low reaction rates, and complicated system configuration and control [3,9,56,80]. A huge potential market (e.g., nearly one trillion of US dollars per year) provides the motivation to solve these issues within a short time. Current progress includes the discovery of thermostable enzymes from extremophiles and low-cost production of recombinant enzymes [80,82,83,84,85,86], engineering redox enzymes that can work on small-size biomimetic cofactors [56,87,88], and accelerating hydrogen generation rates [5,9,24,89].

SFCV is better than BEV

Although the biomass-to-wheel efficiency may be the most important criterion in analyzing future transportation systems, many factors were related with future choices, including energy

storage density, system compactness, fuel costs, infrastructure, safety, operation reliability, environmental costs, resource availability, technology maturity, and improvements potential. Because the energy densities of lithium ion batteries (0.46–0.72 MJ/kg) [90,91] are much lower than those of liquid fuels (~30–40 MJ combustion energy/kg) and sugars (~11–14 MJ electricity/kg sugar) [3,5], BEVs will have a very short driving distance, making the BEV poorly suited for long-distance transportation [32]. If the energy densities of rechargeable batteries were increased by 10-fold in the future, safety concerns would likely come into play, slowing or even preventing wide deployment of such batteries in BEVs. In fact, it is impossible to increase energy densities of lithium rechargeable batteries by 10-fold due to physical limits [90]. Metal/air batteries are supposed to have the highest energy storage density of all batteries [90]. But regeneration of oxidized metals is so energy intensive that metal/air batteries may be too costly for the transport sector. SFCV would have a comparable η_{BTW} with the FC-boiler/BEV scenario but with much longer driving distances based on the same fuel weight (i.e., broader applications). Also, refilling of solid sugar or sugar/water slurry into SFCVs would be much faster and safer than recharging batteries for BEVs or refilling compressed hydrogen for FCVs. If the obstacles to ultra-fast recharging and the life-time of batteries were solved, a huge infrastructure investment would be required for upgrading electrical grids, sockets for quick recharging, power stations, etc. Since SFCV would have ~3.4 times the FTW efficiency of ethanol/ICE-gas (Fig. 6), one kg of sugar (i.e., 17 MG/kg) would release more kinetic energy than one kg of gasoline (i.e., 46.4 MJ/kg) from ICE-gas. Thus, the mass of sugar delivered in the future may be less than the mass delivered by the current liquid gasoline/diesel distribution system. Another advantage is the much shorter sugar slurry transportation distance compared to that of gasoline/diesel, due to local production and distribution. The distribution of sugar would be done based on available goods distribution systems. Since SFCVs use biodegradable enzymes as catalysts, they would greatly decrease the environmental burdens related to BEVs, such as disposing and recycling used batteries.

Beyond BTW

Assessment of any energy system is really challenging because it involves so many factors. Generally speaking, efficiency and cost are usually the two most important criteria. Since thermodynamics (energy efficiency) determine economics in the long term, SFCVs and FC-power/BEV seemed to be long-term winner candidates, but SFCVs have other important advantages. Currently and in the short term, costs mostly determine market acceptance and dominance. But cost analysis is more complicated than energy efficiency analysis, because the former involves direct costs (e.g., fuel, vehicle, etc.), indirect costs (e.g., vehicle service, taxes, subsidies, infrastructure costs for repairing and rebuilding, resource availability, etc.), and hidden costs (e.g., safety, toxicity, waste treatment, greenhouse gas emissions, military expenditures, etc.). In the short term, cellulosic ethanol plus HEV-gas and methane-HEV-gas may be the most promising options.

Potential roles of biomass

It was important to estimate the role of US biomass resources in the future transport sector. The net primary production of biomass in the USA would be approximately 9.83 billion of dry metric tons in 2030, based on the current net primary (biomass) production with an annual growth rate of 1% [92], mainly due to higher photosynthesis yields accompanied with rising CO_2 levels [93,94]. Considering the fact that gasoline/bioethanol consumption in 2008 was approximately 140 billion gallons per year and an assumed annual growth rate of 1%, a switch from ethanol/ICE to sugar/SFCV would require net biomass energy of 11.60 EJ/year in 2030. That is, approximately 700 million metric tons of biomass in 2030, i.e., ~7.1% of calculated annual US biomass (i.e., net primary production including natural ecosystems plus agricultural systems), would be sufficient to meet 100% of transportation fuel needs for light-duty passenger vehicles.

On the prospect of meeting transportation energy needs at acceptable fuel costs, we would like to suggest that short-term or middle-term solutions would be ethanol/butanol/methane plus HEV considering available current fuel distribution infrastructure and enhanced BTW efficiencies. In the long term, SFCVs will likely win over BEVs due to advantageous energy storage densities, safety, infrastructure, and environmental impacts. The great potentials for increasing η_{BTW} values from ethanol-ICE to the future systems (HEV and SFCV) suggest that more efficient utilization of biomass would greatly decrease greenhouse gas emissions, and biomass use could result in more benefits to the environment, rural economy, and national security than originally expected [1]. Through SFCVs, about ~7% of annual US biomass resources may be sufficient to meet 100% of US light-duty transportation fuel needs in the future.

Author Contributions

Conceived and designed the experiments: YPZ. Performed the experiments: WDH. Analyzed the data: WDH YPZ. Wrote the paper: WDH YPZ.

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Simpler Is Better: High-Yield and Potential Low-Cost Biofuels Production through Cell-Free Synthetic Pathway Biotransformation (SyPaB)

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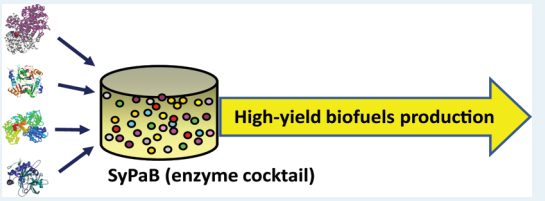
ABSTRACT: The production of biofuels from renewable sugars isolated from plants or produced through artificial photosynthesis would provide a sustainable transportation fuel alternative for decreasing reliance on crude oil, mitigating greenhouse gas emissions, creating new manufacturing jobs, and enhancing national energy security. Since sugar costs usually account for at least 50% of biofuels' selling prices, it is vital to produce desired biofuels with high product yields and at low production costs. Here I suggest high-product yield and potentially low-cost biofuels production through cell-free synthetic enzymatic pathway biotransformation (SyPaB) by in vitro assembly of stable enzymes and (biomimetic) coenzymes. SyPaB can achieve high product yields or high energy efficiencies that living entities cannot achieve. Great potentials of SyPaB, from chiral compounds, biodegradable sugar batteries, sulfur-free jet fuel, hydrogen, sugar hydrogen fuel cell vehicles, high-density electricity storage, to synthetic starch, are motivation to solve the remaining obstacles by using available technologies, such as protein engineering, enzyme immobilization, unit operations, and technology integration. The biotransformation through in vitro assembly of numerous enhanced-performance and stable enzymes in one bioreactor that can last a very long reaction time (e.g., several months or even years) would be an out-of-the-box solution for high-yield and low-cost biofuels production.



KEYWORDS: artificial photosynthesis, biofuels, biological CO_2 fixation, hydrogen, in vitro synthetic biology, biocatalysis and biotransformation, synthetic pathway biotransformation (SyPaB)

1. INTRODUCTION

Biofuels are usually defined as transportation fuels produced from biological resources (e.g., corn kernels, sugar cane, lignocellulosic biomass, and algal biomass) and/or through biological conversions. As compared to the other energy consumption sectors (e.g., industrial, residential, and commercial), transportation fuels that account for approximately 20% of total energy consumption have some special requirements: high energy storage capacity in a small container (e.g., ~50 L), high power output (e.g., ~20−100 kW per vehicle), affordable fuel costs (e.g., $~20−30/GJ), affordable vehicles, low costs for rebuilding the relevant infrastructure, fast charging or refilling of the fuel (e.g., several min per time), safety, and so on.[1−3] Currently, approximately 95% transportation fuels are produced from crude oil. Concerns of depleting crude oil reserves, climate change, national energy security, and wealth transfer are driving the search for sustainable transportation fuel alternatives.[1,3,4]

The production of chemicals mediated by biocatalysts usually has numerous advantages over chemical catalysis, such as higher energy efficiency, higher chemical selectivity (i.e., higher product yield), more modest reaction conditions, and lower costs of bioreactors.[5−7] Different scenarios of biofuels production have been proposed starting from plant biomass, algal biomass, or even CO_2 plus hydrogen or electricity, but nearly all biofuels (secondary energies) originate from the most abundant primary energy—solar energy. Since carbohydrates (e.g., cellulose, hemicellulose, and starch) are the most abundant renewable bioresource (e.g., ~100 billion tons per year), biofuels production through carbohydrates would become a dominant platform in the future. The scope of this perspective is restricted to compare two different biocatalysts, living entities and synthetic cascade enzymes, for the production of the best future biofuel, namely, hydrogen, and the production of synthetic starch from CO_2 but is not involved in bioenergy plants, cellulase engineering, other biofuels production, and algal biofuels. (Note: hydrogen is believed to be the best biofuel in the future because (i) it can be utilized through fuel cells featuring higher energy efficiencies compared to internal combustion engines, (ii) less pollutants are produced, and (iii) it can be produced from diverse energy sources.)

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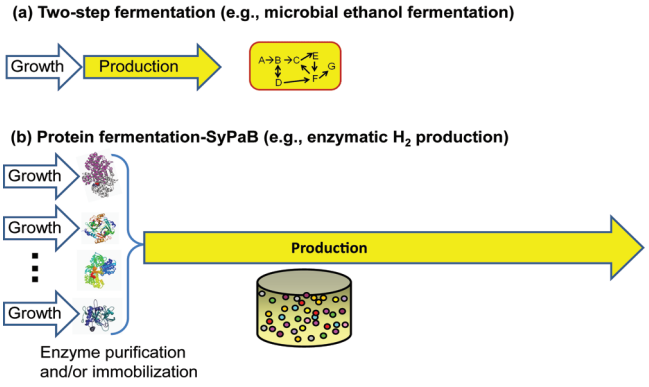

Figure 1. Comparison of microbial two-step biofuels production (a) and a hybrid of microbial fermentation for bulk enzyme production and cell-free synthetic enzymatic biotransformation (SyPaB) (b). Arrows represent microbial fermentation or biotransformation.

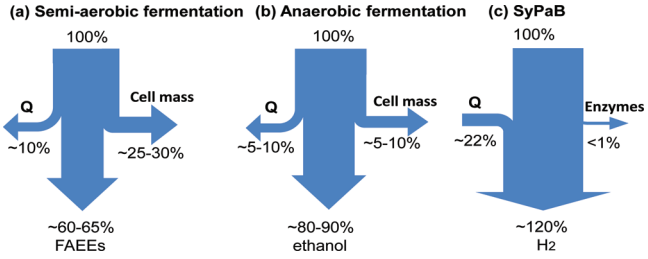

Figure 2. Energy efficiency comparison for fatty acid ethyl esters fermentation by semiaerobic fermentation (a), ethanol fermentation by anaerobic fermentation (b), and hydrogen production by SyPaB (c).

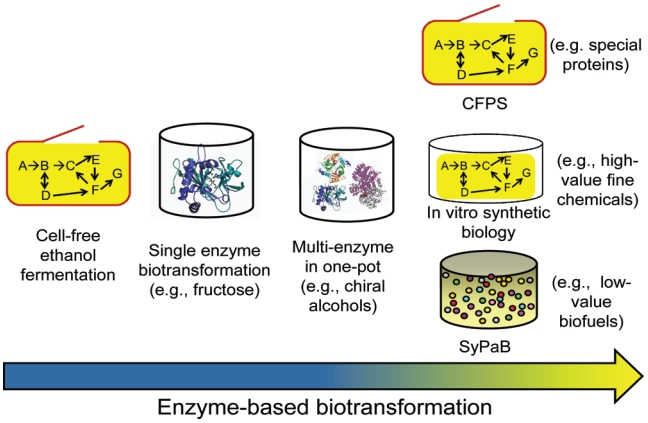

Figure 3. Evolution of enzyme-based biotransformation from cell-free ethanol fermentation (discovery of enzymes), single enzyme biotransformation, multiple-enzyme one pot to cell-free protein synthesis, in vitro synthetic biology, and cell-free synthetic pathway biotransformation in terms of time and increasing system complexity.

Biofuels production R&D is typical of goal-oriented projects with numerous constraints from economical, technological, environmental, social, scalability, competing technologies, and so on. Although so many advanced biofuels, including cellulosic ethanol, long-chain alcohols (e.g., *n*-butanol, iso-butanol), fatty acid ethyl esters, hydrogen, electricity, methane, bioalkanes, and so on, have been produced in laboratories, most of them might not be produced economically in the future. In industrial processes, three key elements—product yield, product titer, and reaction rate—mainly decide process economy. For biofuels production based on available sugars, energy conversion efficiency (or product yield) must be the No.1 cost factor because sugar costs usually account for ~50−70% of prices of mature biofuels.[8−11] The second important factor is product titer, which is closely associated with separation costs, followed by production rate. In it, a default assumption is that reasonable biofuels production rates have been or will be accomplished, for example, ~0.2−1 g sugar consumed per liter per h.

Biofuels can be produced from sugars mediated by (i) growing microbes, (ii) resting cells that are not active in the process of cell division, and (iii) cascade enzymes. When some constituent of cells (e.g., fatty acids) is a desired product, the formation rates of such product are directly related to the rates of cell growth, called growth-associated production. At this situation, growing microbes insist on metabolizing sugars for anabolism (i.e., allocation of sugars to other cell components). Therefore, practical product yields are far below from their theoretical yields.[8,12,13] From the point of view of synthetic biology, both cell growth and undesired product formation by living entities are a dissipation of the task that we want them to do, resulting in relative low product yields. To increase biofuels yields, it is vital to insulate basic anabolism from biofuels production (Figure 1a). In practice, industrial ethanol fermentations are usually conducted in two steps. At the first step, yeasts consume sugars to produce a large amount of cell mass with oxygen supplies; at the second step, yeasts produce high-yield ethanol from glucose in the absence of oxygen. When ethanol titer is high, it can stop yeast growth so that yeasts turn to resting cells that produce ethanol only without significant synthesis of cell mass[14] (Figure 1a). Here I extended the concept of high-yield resting cell biotransformation to high-yield cell-free synthetic pathway biotransformation (SyPaB) that can implement complicated biochemical reactions by the in vitro assembly of numerous enzymes and coenzymes.[9,15−17] In SyPaB, the insulation of cell growth from product formation is implemented by process operations (Figure 1b).

An analysis based on thermodynamics and bioenergetics was conducted for assessing upper limits of energy efficiency for the production of fatty acid ethyl esters (FAEEs) by semiaerobic fermentation, ethanol by anaerobic fermentation, and hydrogen by SyPaB (Figure 2).[8] According to their biochemical pathways and thermodynamics, 100% product yields result in ~10% combustion energy loss for FAEEs, ~5% loss for ethanol, and ~22% gain for hydrogen.[8,18,19] Since a fraction of sugar must be consumed for biocatalyst synthesis, potential yields of biofuels should be lower than their theoretical yields. An imbalance of coenzymes in microbial FAEEs production leads to a significant fraction of carbohydrate loss for the synthesis of cell mass in semiaerobic fermentation. As a result, only 60−65% of the combustion energy in sugar would be converted to FAEEs. Ethanol fermentation has much better energy-retaining efficiencies because of (i) anaerobic fermentation and (ii) uncoupling of cell growth and product formation. Therefore, ethanol is a very good liquid biofuel now. The best case would be hydrogen produced by SyPaB because of 22% of extra enthalpy gain by absorbing waste heat (i.e., the combustion energy of hydrogen is more than that of sugar) and a very small amount of sugar consumed for the synthesis of cascade enzymes when enzymes

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have total turnover number (TTN) values of 10^7-10^8 mol product per mol enzyme.[8,15,20]

In this perspective, I present an out-of-the-box solution for a high-yield and potentially low-cost biofuels production platform, SyPaB, featuring very high product yields and fast reaction rates that can insulate protein synthesis from biofuels production, review the brief history of enzyme-based biotransformations, argue SyPaB as a new low-cost biomanufacturing platform, and discuss challenges and opportunities of SyPaB.

2. HISTORY OF ENZYME-BASED BIOTRANSFORMATIONS

Long before people had a clue about the nature of biotransformation, certain properties of microorganisms had been long exploited for commercial processes, such as in the production of beer, wine, vinegar, soy sauce, and cheese, and the preservation of vegetables by pickling. Central to the rational use of biocatalysts has been a stream of theoretical understanding of the nature of living biocatalysts and related enzymes. The developments of enzyme-based biotransformations (Figure 3) can be divided roughly into four phases:

Phase 1 (1897). Recognition of biotransformation occurrence in the absence of living cells (cell-free ethanol fermentation by Eduard Bucher, Nobel Prize in Chemistry, 1907).[9] Later, more studies were focused on studies of enzymes responsible for natural enzymatic pathways in basic metabolisms. For example, Otto Fritz Meyerhof won the Nobel Prize in Physiology or Medicine in 1922 for his elucidation of the glycolytic pathway.[21] Even now, in vitro reconstitution of natural pathways is still an important tool to understand and discover in vivo complicated biochemical reactions or pathways.[22,23]

Phase 2 (1960s). Utilization of one enzyme for simple biotransformation.[5,24] Clearly, the use of isolated enzymes for the production of chemicals has a much shorter history than microbial fermentation. Invertase may be the first immobilized enzyme used commercially for the production of Golden Syrup by Tate & Lyle in World War II. Industrial process for L-amino acid production by soluble aminoacylase was developed in 1954. In 1969, Tanabe Seiyaku Co. (Japan) started the industrial production of L-methionine by using immobilized aminoacylase in a packed bed reactor. In 1967, the Clinton Corn Processing Company (U.S.A.) was the first to produce fructose corn syrup by glucose isomerase. Currently, immobilized glucose isomerase Sweetzyme T (Novo, Denmark) is packed into columns for conversion of glucose into fructose. The longest working lifetime of immobilized glucose isomerase is 687 days at 55 °C and pH 7.5 by Kato Kagaku (Japan). Now, annual enzymatic fructose production from glucose exceeds 9 million tons.[24] Enzymatic acrylamide production was initiated in 1985. Currently, more than 100,000 tons of acrylamide is produced by using immobilized nitrile hydratases per year.[24] Discovery and utilization of thermoenzymes, protein engineering including directed evolution, rational design and their combination, high-cell density fermentation for low-cost recombinant protein production, and enzyme immobilization have enabled the production of very stable recombinant enzyme at very low costs.[25−28]

Phase 3 (1990s). Utilization of multienzyme one pot for relatively complicated biotransformation because most enzymes can function under similar conditions. Multienzyme one pot has numerous benefits: fewer unit operations, smaller reactor volume, higher volumetric and space-time yields, shorter cycle times, and less waste generated. Also, by coupling steps together, unfavorable equilibria can be driven toward the formation of desired products.[9,29,30] For cofactor-dependent enzyme reactions, it is not economically feasible to continuously provide costly cofactors in biomanufacturing. Therefore, in situ NAD(P)H-regenerated by another enzyme is becoming more and more accepted, especially for the synthesis of high-value chiral compounds in the pharmaceutical industry.[17,31,32] NAD(P)H is usually generated by using a pair of a hydrogen-donor substrate and a single enzyme, including formate/formate dehydrogenase,[33] glucose/glucose dehydrogenase,[34] glucose-6-phosphate/glucose-6-phosphate dehydrogenase,[26] dihydrogen/hydrogenase,[35] and phosphite/phosphite dehydrogenase.[36] In another case, enzymatic hydrolysis of crystalline cellulose require a synergetic action of endoglucanases, cellobiohydrolases, and beta-glucosidases.[37−39] In the organic chemistry field, the synthesis of monosaccharides, activated monosaccharides, oligosaccharides, and glycopeptides by using multienzyme one pot has been intensively investigated.[40−46]

Phase 4 (2000s). Utilization of numerous cascade enzymes for very complicated biotransformation. It includes three representative directions: (1) cell-free protein synthesis (CFPS), which utilizes natural protein synthesis systems in cell lysates for fast synthesis of proteins for research purpose and the production of high-value antibodies or other proteins,[47,48] (2) in vitro synthetic biology for the production of high-value products,[25,49−52] and (3) synthetic pathway biotransformation (SyPaB) for low-value biofuels production.[9,15,17] Different from CFPS and high-value product formation, SyPaB must have balanced cofactors and ATP in vitro.[17] In addition, thermodynamics must be analyzed to ensure designed non-natural processes to take place as expected. The development cycle of SyPaB is composed of five parts: (i) pathway reconstruction, (ii) enzyme selection, (iii) enzyme engineering, (iv) enzyme production, and (v) bioprocess engineering.[9,15,17] Whole SyPaB processes can be improved in an iterative manner, gradually leading to a low-cost industrial bioprocess.[9,15,17] The SyPaB technology has successfully achieved some breakthroughs that neither microbes nor chemical catalysts could implement before, such as production of nearly 12 mol of hydrogen from per mol of anhydroglucose and water,[19,53] ultrahigh-yield regeneration of NAD(P)H in microbe-toxic biomass hydrolysate,[20] enzymatic conversion of ethanol and CO_2 to lactate,[54] and so on.

3. BIOCATALYSTS: LIVING ENTITIES VERSUS SYPAB

Although SyPaB and living entities are responsible for transforming similar-level complicated biochemical reactions, SyPaB featuring high product yields and fast reaction rates enable it to play more important roles in biofuels production because (energy) conversion efficiencies will be important to decide their production economics in a long-term[8] and their reaction rates will be vital to their potential applications.[1,55] Here we present two SyPaB examples, which do much better than do natural living entities.

3.1. Hydrogen Production from Sugars. The global biosphere produces more than 250 million tons of biohydrogen per year.[56] Most hydrogen arises from anaerobic fermentation of carbohydrate previously fixed by photosynthesis, followed by its consumption along with CO_2 or organic acid reduction by methanogenic archaebacteria. On oceanic continental shelves

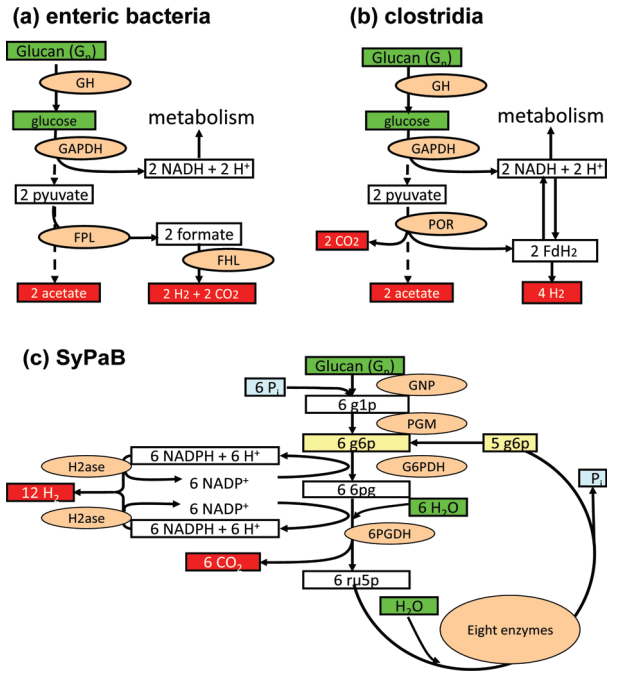

Figure 4. Scheme of microbial hydrogen production by enteric bacteria (a), clostridia (b), and by SyPaB (c).

and in permafrost regions, methane has been accumulated extensively as methane hydrate deposits, which exceed petroleum, coal, and natural gas deposits combined. In other locales, methane is released to the atmosphere, a much stronger greenhouse gas than carbon dioxide.

Natural microorganisms can produce hydrogen from sugars through different pathways.[38,57−59] The upper limit of hydrogen yield for living entities is 4 mol of H_2 produced per mol of glucose equivalent consumed plus 2 acetic acids, called the Thauer limit (eq 1).[58,59]

$$C_6H_{12}O_6(aq) + 2H_2O(l) \rightarrow 4H_2(g) + 2CO_2(g) + 2C_2H_4O_2(l) \quad (1)$$

Enteric microorganisms include facultative anaerobic bacteria, such as *Enterobacter aerogenes, Enterobacter cloacae,* and *Escherichia coli*. Since they can grow under aerobic conditions for high-cell mass concentrations, such high-cell masses result in extraordinarily high volumetric H_2 productivities. However, specific H_2 yields of enteric bacteria are relatively low, usually less than two mol of H_2 per mol of glucose because of their central metabolism, where hydrogen is generated from pyruvate−formate lyase and formate hydrogen lyase[60] (Figure 4a). NADH is generated from the glycolytic pathway, but this coenzyme is not a favorable electron carrier for hydrogen generation at moderate temperatures. The clostridia are obligate anaerobes capable of producing organic solvents as well as H_2 through a mixed acid pathway (Figure 4b). These microorganisms are the predominant organisms in mixed microflora capable of producing H_2 from biomass waste treatment.[61] Different from enteric bacteria, H_2 production by many clostridia species is catalyzed by the combination of pyruvate:ferredoxin oxidoreductases (POR) and Fe-only hydrogenase.[62] NADH can donate electrons to ferredoxin by NADH:ferredoxin oxidoreductase.[38] Several clostridial species have been evaluated for their potential as biohydrogen producers.[61] Hyperthermophiles can produce nearly 4 mol of H_2 produced per mol of glucose equivalent, albeit at lower volumetric productivities than observed for mesophilic bacteria.[57] In spite of intensive efforts in metabolic engineering and synthetic biology, none of natural or engineered microorganisms can produce hydrogen more than the Thauer limit.[57,63−66]

To break the Thauer limit, a non-natural synthetic pathway has been designed to split water by using the chemical energy in starch.[19] As a result, far more than 4 mol of hydrogen per mol of glucose unit from starch and water is produced.[19]

$$C_6H_{10}O_5(aq) + 7H_2O(l) \rightarrow 12H_2(g) + 6CO_2(g) \quad (2)$$

This non-natural synthetic catabolic pathway is composed of 13 enzymes together (Figure 4c). The pathway contains four biocatalytic modules: (i) a chain-shortening phosphorylation reaction for producing glucose-1-phosphate (g1p) catalyzed by glucan phosphorylase (eq 3); (ii) generation of glucose-6-phosphate (g6p) from g1p catalyzed by phosphoglucomutase (eq 4); (iii) generation of 12 NADPH from g6p through a pentose phosphate pathway plus four enzymes in the glycolysis and gluconeogenesis pathways (eq 5); and (iv) generation of hydrogen from NADPH catalyzed by hydrogenase (eq 6).

$$(C_6H_{10}O_5)_n + P_i \rightleftharpoons (C_6H_{10}O_5)_{n-1} + g1p \quad (3)$$

$$g1p \rightleftharpoons g6p \quad (4)$$

$$g6p + 12NADP^+ + 7H_2O \rightleftharpoons 12NADPH + 12H^+ + 6CO_2 + P_i \quad (5)$$

$$12NADPH + 12H^+ \rightleftharpoons 12H_2 + 12NADP^+ \quad (6)$$

Thermodynamic analysis suggests that the overall reactions from starch or cellulosic materials and water are spontaneous and endothermic (i.e., $\Delta G^\circ = -49.8$ kJ/mol and $\Delta H^\circ = +598$ kJ/mol).[19,53] Such reactions are driven by entropy gains rather than enthalpy losses. These entropy-driven chemical reactions can generate the chemical energy in the form of hydrogen more than the chemical energy in polysaccharides by absorbing ambient-temperature thermal energy.[19,53] The removal of gaseous products, H_2 and CO_2, from the aqueous phase under mild reaction conditions (<100 °C and ~1 atm) favors the unidirectional reactions for the formation of hydrogen.[19,53] Similarly, another entropy-driven bioreaction is $C_2H_4O_2(aq) \rightarrow CH_4(g) + CO_2(g)$ mediated by methanogenesis microorganisms, resulting in 1.7% combustion energy gain. Two spontaneous endothermic chemical reactions are $N_2O_5(s) \rightarrow 2\,NO_2(g) + {}^1/_2O_2(g)$ and $Ba(OH)_2 \cdot 8H_2O(s) + 2NH_4SCN(s) \rightarrow Ba(SCN)_2(aq) + 2NH_3(aq) + 10H_2O(l)$.[9] All of the above entropy-driven reactions involve phase changes from more orderly to less orderly.

3.2. Biological CO_2 Fixation. Carbon dioxide can be biologically fixed by plants, microorganisms, and animals. Most plants fix carbon dioxide by using chloroplasts through the reductive pentose-phosphate cycle, that is, the Calvin−Benson cycle. Microorganisms can fix CO_2 through six pathways: the reductive citric acid cycle,[67] the reductive acetyl-CoA pathway (Wood−Ljungdahl pathway),[68] the 3-hydroxypropionate pathway,[69] the 3-hydroxypropionate-4-hydroxybutyrate cycle, and dicarboxylate-4-hydroxylbutyrate cycle.[70] Sometimes, animal tissues, such

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as liver cells, have been found to fix CO_2 to produce cell constituents (e.g., glycogen).[71] All of natural biological CO_2 fixation pathways require 12 mol of the reduced cofactor (NADPH) or its equivalents plus several mol of ATP for the generation of one mol of glucose from 6 mol of CO_2. The ATP number consumed depends on the pathways in microorganisms and plants, ranging from 2 to 30.[70,72] Here ATP is an extra energy driving force for implementing thermodynamically-unfavorable reactions because most times CO_2 concentrations in the environments are very low. When high concentration of CO_2 is available, the number of ATP consumed per glucose unit may be decreased greatly.

Plant photosynthesis utilizes intermittent low-energy concentration solar energy (e.g., ~170 W/m^2) and fixes CO_2 in the form of carbohydrate. But natural plant photosynthesis has pretty low energy efficiencies from solar energy to chemical energy of 4.6−6.0% (theoretical), ~3−4% (peak), ~1−2% (dedicated crops), and ~0.2−0.3% (global average).[73−75] Such low efficiencies are mainly attributed to four factors: (i) narrow light absorption spectrum by chlorophylls, (ii) unmatched reaction rates between light reactions and dark reactions, (iii) relatively low efficiencies of carbohydrate synthesis, and (iv) carbohydrate losses because of respiration of living entities.[73−76]

To surpass low-efficiency plant photosynthesis for CO_2 fixation, another potential application of SyPaB is to fix CO_2 through a non-natural ATP-neutral high-efficiency pathway[77] (Figure 4, eq 7)

$$8CO_2(g) + 18H_2(g) \rightarrow C_6H_{10}O_5(s) + C_2H_6O(l) + 10H_2O(l) \quad (7)$$

where the inputs are CO_2 and hydrogen; the outputs are water-insoluble amylose (linear starch), volatile ethanol (C_2H_6O), and water.

The hypothetical hydrogen/CO_2-to-carbohydrate process is composed of six biocatalytic modules, including

(1) NADH is generated from hydrogen by using hydrogenase (eq 8)[78,79]

$$18NAD^+ + 18H_2 \rightleftharpoons 18NADH + 18H^+ \quad (8)$$

(2) CO_2 fixation to formaldehyde (CH_2O) mediated by formate dehydrogenase and formaldehyde dehydrogenase (eq 9),[80−82]

$$9CO_2 + 18NADH + 18H^+ \rightleftharpoons 9CH_2O + 9H_2O + 18NAD^+ \quad (9)$$

(3) conversion of formaldehyde to fructose-6-phosphate (f6p) by 3-hexulose-6-phosphate synthase and hexulose phosphate isomerase from the ribulose monophosphate pathway (eq 10),[83,84]

$$9CH_2O + 9ru5p \rightleftharpoons 9f6p \quad (10)$$

(4) ribulose-5-phosphate (ru5p) regeneration by the eight enzymes from the nonoxidative pentose phosphate pathway (eq 11),[19,72]

$$8f6p + 2ATP \rightarrow 9ru5p + g3p + 2ADP \quad (11)$$

(5) ethanol production from glyceraldehydes-3-phosphate (g3p) by the seven enzymes from the glycolysis and ethanogenesis pathway (eq 12),[72]

$$g3p + P_i + 2ADP \rightarrow C_2H_6O + CO_2 + H_2O + 2ATP \quad (12)$$

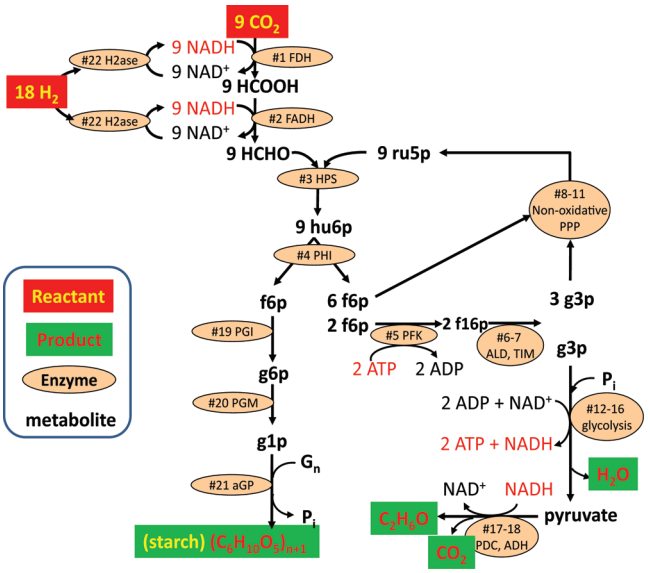

Figure 5. In vitro ATP-balanced synthetic pathway of CO_2 fixation by using hydrogen for the production of synthetic starch and ethanol.

(6) starch (amylose, a linear α-1,4-glucosidic bond starch) lengthening reaction mediated by starch phosphorylase along with phosphoglucose isomerase and phosphoglucomutase (eq 13),[19,72]

$$f6p + (C_6H_{10}O_5)_n \rightleftharpoons (C_6H_{10}O_5)_{n+1} + P_i \quad (13)$$

The combination of eqs 8−13 results in eq 7 with an energy conversion efficiency of 81%.[77] The standard Gibbs free energy of eq 7 is −54.5 kJ/mol, implying that the above reaction may occur spontaneously under standard conditions. The overall reaction could be operative since (i) nearly each reaction is reversible, except 6-phosphofructokinase and pyruvate kinase, both of which control the overall reaction direction, (ii) each module (eqs 8−13) involving several enzymatic steps has been implemented successfully in the literature, and (iii) the Gibbs free energy is negative. This process can drive forward the desired products through several process operations: (i) high-pressure and high concentration CO_2 from a power station or a CO_2 storage site is used for a high driving force for this artificial photosynthesis, (ii) the amylose-lengthening reaction occurs on the nonreducing ends of amylose and amylose is more insoluble in the presence of ethanol, and (iii) ethanol can be stripped from the aqueous phase. Instead of putting all of enzymes in SyPaB in one reactor, it is possible to separate several cascade reactions into several bioreactors in series, as demonstrated in the synthesis of D-ribulose-1,5-bisphosphate from 3-phospho-glycerate.[85] In the starch synthesis step (eq 13), this reaction may be run like solid-phase synthesis, where anhydroglucose units are added on the nonreducing ends of amylose one by one.

The major potential applications of such artificial photosynthesis could be the storage of low-cost renewable hydrogen or electricity in the form of starch and ethanol on a large scale

Table 1. Challenges on SyPaB Technology and Their Respective Solutions and Supportive Examples

challenge	solution	example	ref.
enzyme instability	utilization of thermoenzymes	Taq polymerase, amylase, glucose isomerase	121,122
	protein engineering (directed evolution and rational design)	subtilisin, cellulase	123−125
	enzyme immobilization	immobilized glucose isomerase, immobilized phosphoglucose isomerase	5,126
	TTN value $>10^7$	CthPGI, CthPGM, Tm6PGDH, TmFBP [a]	26,28,94,95
costly enzymes	high-cell density microbial fermentation production	cellulase ($5/kg), amylase ($∼10/kg), Hyperthermophilic 6PGDH	14,26,37
	recombinant overexpression by *E. coli*	*P. furiosus* hydrogenase, CthPGI, CthPGM, Tm6PGDH, TmFBP,	26,28,94,95,127
	simple scalable purification techniques (e.g., heat precipitation, $(NH_4)_2SO_4$ precipitation, adsorption/desorption)	heat precipitation (Tm6PGDH), one-step CthPGI purification and immobilization	14,26,28,96,97
costly and labile coenzymes	coenzyme immobilization and recycling	chiral alcohol synthesis in biopharmaceutical industry	128,129
	stable and low-cost biomimetic coenzyme replacement	P450, horse peroxidase, alcohol dehydrogenase	100,101,103,104
lack of thermoenzyme library	meta-genomics, bioinformatics tools, robotic automation, and high throughput cloning	screening ∼500 recombinant enzymes in one biocatalysis reaction >1400 *T. thermophilus* HB8 thermoenzyme library	14
different optimal conditions for different enzymes	reaction conditions compromised	sugar-to-hydrogen, biohydrogenation	19,20,53
	numerous enzymes obtained from one source or modify them	*T. thermophilus* HB8 thermoenzyme library	14
scalability potential	production of 75 million tons of H_2 replacing 450 million tons of gasoline (i.e., 150 billion gallons)	∼250,000 tons of enzyme mixtures (i.e., ∼300 kg of H_2 per kg of enzyme mixture) [b]	120

[a] CthPGI, *C. thermocellum* phosphoglucose isomerase; CthPGM, *C. thermocellum* phosphoglucomutase; Tm6PGDH, *T. maritima* 6-phosphogluconate dehydrogenase; and TmFBP, *T. maritima* fructose-fructose-1,6-bisphosphatase. [b] One kg of enzyme mixture can produce 300 kg of hydrogen based on two assumptions: (i) all enzymes have TTN values of 30,000,000 mol product per mol enzyme and (ii) the average molecular weight of the enzyme mixture is 50,000.[20]

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Table 2. Analysis of Potential Hydrogen Rate Increases for Sugar-to-Hydrogen Mediated by SyPaB

technology	potential fold	ref.	predicted fold[a]
increasing reaction temperatures from 30 to 80 °C or even higher	32	Q10 effect for hyperthermophilic hydrogenase[b130]	4−20
increasing the use of enzymes responsible for rate-limiting reactions	10	53	2−5
increasing overall enzyme concentration	10	106	5
increasing substrate concentration by 50-fold	10	53	5
creating metabolite channeling among cascade enzymes	∼2−50	95,131,132	2
increasing catalytic efficiency of enzymes	∼10		
overall accelerating rates	640,000−32,000,000		500−5,000

[a] Predicted folds based on each technology may change greatly. It is feasible to increase reaction rates by 3000-fold to be the same level as compared to the highest microbial hydrogen generation rates.[106] [b] *P. furiosus* hydrogenase responsible for the rate-limited step in the sugar-to-hydrogen production, exhibited approximately 1% of its maximum activity at ∼30 °C. Increasing reaction temperature along with the use of other thermoenzymes would accelerate hydrogen generation rates greatly.

and the production of feed and food in emergency cases, such as volcanic winter. A combination of high efficiency solar cells with solar-to-electricity efficiencies of 18−42%,[86] water electrolysis with electricity-to-hydrogen efficiencies of ∼85%,[87] and carbohydrate generation from H_2 and CO_2 with an efficiency of ∼80% here would have overall solar energy-to-carbohydrate efficiencies from 12 to 29%, much higher than those of natural plant photosynthesis.[73,75] The much higher efficiencies of this artificial photosynthesis are mainly attributed to (i) higher efficiency solar cells that can utilize a broader wavelength range of solar insolation, (ii) no respiration (energy) losses in cell-free biocatalysis systems, and (iii) higher-energy efficiency synthetic pathway of starch (Figure 5). Since solar/wind electricity can be easily collected by wires and be distributed by grids, it would be feasible to produce synthetic starch 24/7 at well-controlled bioreactors. More appealing, this artificial photosynthesis does not require a large amount of water for plant transpiration, resulting in potential conservation of fresh water by about 500-fold or higher.[88,89] The pollutants generated from bioreactors can be treated more easily than those from agricultural land because they are point pollution sources.[90] Modern farming requires significantly high inputs from nutrients (e.g., nitrogen and phosphorus), herbicides, and pesticides for high crop productivities.[91] Only a fraction of fertilizers (e.g., ∼30−50%) are utilized by plants, resulting in severe nonpoint water pollution from agricultural land.[92] Waste water pretreatment for bioreactors would be much easier than those from agricultural land.

Approximately 10−60 fold increases in area-specific starch productivity and ∼500−1000 fold water reduction per weight of starch synthesis through this artificial photosynthesis would drastically decrease land uses for biofuels production and reduce or eliminate land/water competition with food and feed production. Also, the conversion of starch to biofuels and value-added chemicals is much more easy than that of nonfood biomass.[38,73,93]

4. CHALLENGES AND OPPORTUNITIES

Construction of in vitro synthetic enzymatic pathways is much easier than modification of living biological entities so that in vitro reconstitution of enzymatic pathways has long been used for understanding natural pathways.[22,23] In the future, in vitro synthetic cascade enzymes would become a low-cost biomanufacturing platform, where product yield is the most critical factor for economically viable production of biofuels. Different from living biological entities operated far from thermodynamic equilibrium and their complicated regulation mechanisms, which are being elucidated by intensive efforts of systems biology and synthetic biology, cell-free systems can be accessed, regulated, operated, and scaled up easily. For example, it is relatively easy to get very high product yields, although all of the enzymes are obtained from different sources and their optimal conditions are not matched well.[20,50,53]

The challenges or doubts of low-cost biomanufacturing SyPaB are attributed to a fixed paradigm of most bioengineers and scientists. The possible causes include (i) enzyme instability, (ii) costly enzymes, (iii) costly and labile coenzymes, (iv) a lack of stable enzymes, (v) different optimal conditions for different enzymes, and (vi) scalability potential.[9,14] To address the above challenges, the respective solutions and supportive examples are listed in Table 1. For example, enzyme instability can be addressed by thermoenzymes, protein engineering through directed evolution and rational design, enzyme immobilization, and their combinations. The previous economic analyses suggest that enzyme costs would be minimal when total turnover numbers (TTN) of all enzymes are larger than 10^7−10^8 mol of product per mol of enzyme.[14,15,20] In practice, it is very feasible to obtain enzymes with such high TTN values from natural thermoenzymes, for example, *Clostridium thermocellum* phosphoglucomutase,[94] *Thermotoga maritima* 6-phosphogluconate dehydrogenase,[26] *T. maritima* fructose-1,6-bisphosphatase,[95] and *C. thermocellum* phosphoglucose isomerase.[28] With respect to costly enzyme, bulk industrial enzymes can be produced and obtained at very low costs, for example, $∼5 per kg of crude protease produced by *Bacillus subtilis*, $5−10 per kg of cellulase produced by *Trichoderma* spp., and tens of U.S. dollars per kg of recombinant proteins produced in *E. coli*.[14] Several low-cost scalable protein purification approaches are available, for example, simple centrifugation for secretory enzymes, adsorption/desorption on low-cost cellulosic materials,[96,97] heat precipitation for thermostable enzymes,[26,98] ammonia precipitation,[14,99] and one-step enzyme purification and immobilization.[28] Therefore, purification costs for bulk recombinant thermoenzymes would become minor.

Currently, the largest obstacle to SyPaB may be costly coenzymes, NADH and NADPH. The labile coenzyme issue can be addressed by the use of low-cost and stable NAD biomimetic coenzymes. But this research area is in its infancy[100,101] because there were no large markets before. Several redox enzymes (e.g., P450 and alcohol dehydrogenase) have been engineered for better performance on biomimetic coenzymes.[102−104] With developments in (i) engineered oxidoreductases that can use biomimetic NAD coenzymes and (ii) stable enzymes as building blocks of SyPaB, we

Table 3. Selected SyPaB-Based Applications, As Compared to Competing Technologies, Their Technology Readiness Levels (TRL) for the Y-12 National Security Complex,[108] Their Remaining Obstacles, and Respective Solutions

application	competing technology	market size* (US $/year)	TRL	remaining obstacle	solution	ref.
biosynthesis of chiral drugs via biohydrogenation	one-enzyme NAD(P)H regeneration	~ billions	TRL 6	separation of metabolites/products with enzymes	enzyme immobilization, membrane reactor	20,36
environmentally friendly sugar batteries (enzymatic biofuel cells)	primary batteries, rechargeable batteries, DMFC	~ 2 billion	TRL 4	low power output, incomplete oxidation, short lifetime	system optimization, nanobiotechnology, cascade pathways, thermoenzymes, enzyme engineering and immobilization	9,110,111
sugary H_2 for local hydrogen users	made from natural gas and coal, or biomass, solar, or wind energy	~20 billion (e.g., ~8 million tons of H_2)	TRL 4	enzyme stability, enzyme costs, labile coenzymes, slow reaction rates	Tables 1 and 2	9,14,19,53
sulfur-free jet biofuel	microbial fermentations, FT process, pyrolysis	~ 50 billion (e.g., 75 million tons of jet fuel)	TRL 3	*ditto* as biohydrogenation, metabolite, and enzyme removal	Table 1, membrane reactor	9,14,20
electricity generators	Diesel electricity generators	~ billions	TRL 2	*ditto* as sugary H_2	Tables 1 and 2	1
sugar fuel cell vehicles (SFCV)	BEV [a] FCV ICE	~500 billion (e.g., 450 million tons of gasoline)	TRL 2	*ditto* as sugary H_2 slow reaction rate	Tables 1 and 2	1,3,16
CO_2 fixation for starch production	dedicated bioenergy plants, mass electricity storage	NA	TRL 2	*ditto* as enzymatic fuel cells	Tables 1 and 2	77

* U.S. market only. [a] BEV, battery electric vehicle; FCV, (hydrogen) fuel cell vehicle; ICE, internal combustion engineer-based vehicle.[120]

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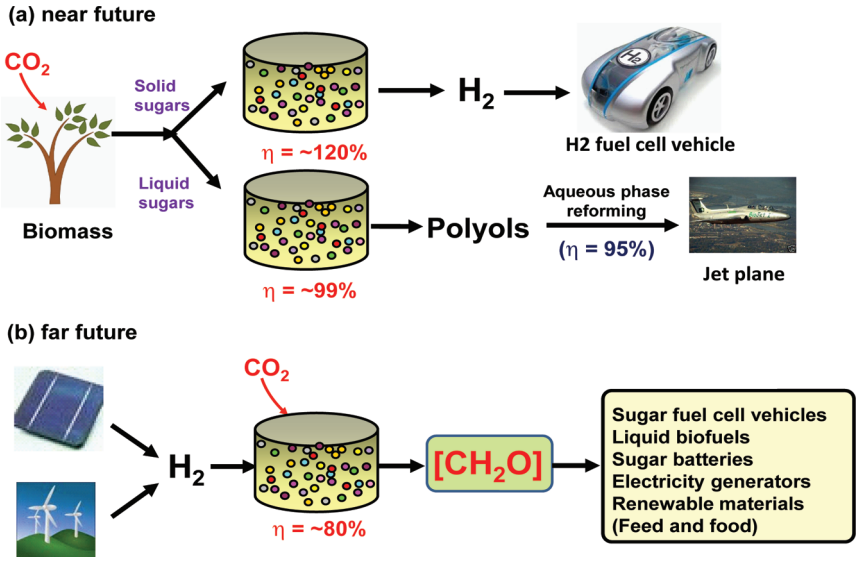

Figure 6. Different biofuels scenarios based on plant biomass through natural photosynthesis (near future) and starch produced by artificial photosynthesis (far future), where high-yield and low-cost SyPaB would have a central role for different biofuels production. The data in red represent energy efficiencies mediated by SyPaB featuring ~99% mass conversion.

estimate that ultimate hydrogen production costs may decrease to ~$1.50 per kg of hydrogen, where carbohydrate ($0.22/kg) accounts for ~95% of its production costs, in part because biohydrogen has very low separation and purification costs and the other chemicals in reactors can be recycled.[14,15]

Enzymatic reactions are usually faster than microbial fermentations[9,105] mainly because neither the dilution of biomacromolecules (e.g., DNA, RNA, other proteins, etc.) nor the mass transfer barriers resulted from the cellular membrane.[1,14] Current enzymatic hydrogen generation rates are comparable with those of anaerobic hydrogen fermentation and are much faster than photobiological hydrogen fermentation.[53] As compared to the highest microbial hydrogen production rates (i.e., 23.6 g H_2/L/h) in the literature,[106] the current enzymatic hydrogen rate[53] would have a potential of ~3000-fold reaction rate increases. Table 2 shows potential methods for increasing reaction rates for sugary hydrogen mediated by SyPaB. They are: (i) increasing reaction temperatures, (ii) increasing the use of enzymes responsible for rate-limiting reactions, (iii) increasing substrate concentrations, (iv) increasing overall enzyme concentrations, (v) accelerating the reaction rates by metabolite (product) channeling, and (vi) increasing the catalytic efficiency of enzymes to catalytically perfect enzymes. With more collaboration among biologists, chemists, and engineers all round the world and system optimization, the reaction rates of SyPaB would be accelerated by several orders of magnitude.[1] In partial support to this prediction, power densities of microbial fuel cells have been enhanced by nearly 10,000,000 fold through intensive efforts during the past one and a half decade.[107]

SyPaB-based applications are increasing greatly. Table 3 presents several potential applications, as compared to their competing technologies, technology readiness levels (TRL),[108] remaining obstacles, and respective solutions. Since each application has its unique market, it has different technology challenges (Table 3). For example, a promising application is enzymatic fuel cells (EFC) powering (low-power) portable electronics, such as cellular phones and MP3 players.[105,109,110] Several big companies (e.g., Sony and Nokia) and small companies (e.g., Gate Fuels and Akermin) are developing enzymatic fuel cells. To our knowledge, the highest power densities of enzymatic fuel cells based on sugar are about 5−10 mW/cm^2 of anode, sufficient to power a Sony Walkman.[111,112] To increase fuel utilization efficiency, cascade enzymes are usually employed.[110,113−115] Complete conversion of sugar energy to electricity would have 4-fold benefits: high energy utilization efficiency, high energy storage density, low product inhibition, and high power density.[9,105,116] It is estimated that complete oxidization of a 20% sugar/water solution (17 MJ/kg sugar ×20%) would lead to energy storage densities of up to 1.7 MJ (i.e., 470 Wh) electricity per kg of the fuel solution based on ~100% Coulombic efficiency and ~50% voltage efficiency. Clearly, such high-energy density biodegradable EFCs might replace some primary batteries and secondary batteries in the future.[55,117]

5. BIOFUELS PERSPECTIVE

Enzyme-based biotransformations are evolving from a single enzyme to multienzyme one pot to synthetic cascade enzymes. SyPaB features unique advantages: great engineering flexibility, high product yields, fast reaction rates, broad reaction conditions (e.g., high temperature and/or low pH), easy operation and control, and tolerance of microorganism-toxic compounds.[9,15,16,20] Therefore, SyPaB would play more important roles in some yield-sensitive applications, such as biofuels production, because thermodynamics (energy efficiency) determines economics (cost) in the long term.[118]

What biofuels would be short-term (e.g., 5 years), middle-term (e.g., 10−20 years), and long-term (e.g., > 20 years) winners is under debate. But it is worth pointing out that high-yield conversion would defeat low-yield conversion eventually because of a megatrend of increasing energy utilization efficiency. In the future, transportation fuels could mainly consist of hydrogen from carbohydrates for light-duty vehicles, electricity from renewable energy sources for short-distance vehicles, and high-energy density liquid biofuels (e.g., hydrocarbons and

butanol) made from biomass for jet planes.[1,119] On the basis of available biomass resources and pretreatment (Figure 6a), liquid hemicellulose sugars and solid cellulosic materials may be converted to jet fuel and hydrogen through high-yield SyPaB, respectively. Liquid jet fuel can be produced through a hybrid of high-yield SyPaB and aqueous phase reforming with an overall energy retaining efficiency (~95%), much higher than fatty acid ester fermentation (~60−65%) and butanol fermentation (~85%).[8,20] Cellulosic materials can be converted to hydrogen in local stations for providing hydrogen for proton exchange membrane fuel cell vehicles.[3,14] In the far future, synthetic starch used for electricity/hydrogen storage (e.g., > 8 mass H_2% or 11−14 MJ electricity/kg starch) may be generated through artificial photosynthesis with an hydrogen-to-starch efficiency of ~80% mediated by SyPaB. Also, starch can be converted back to hydrogen or electricity for different applications. For example, fuel cell-based sugar vehicles that would store starch as a high-density hydrogen carrier might become ultrahigh energy efficiency prime movers.[1,3,120]

In a word, great potentials of high-yield SyPaB (Table 3) would motivate the transformation of basic research to real applications by integrating well-known technologies (Table 1). The maturation of genomics, molecular biology, techniques for enzyme engineering, low-cost enzyme production, purification, and immobilization has led to highly efficient, tunable enzymes tailored for specific large-scale industrial production. The biotransformation through in vitro assembly of numerous enhanced performance and stable enzymes in one bioreactor that can last a very long reaction time (e.g., several months or even years) would become a disruptive technology for low-cost biomanufacturing, especially for the production of biofuels where product yield is the most important cost factor.

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Jonathan Taub
LOS ANGELES CA

I believe that research should be done on adapting oily algae DNA to grow with less light to facilitate growing in large tanks to make production easier and to target algae that can be grown in salt and/or waste water and possibly used to treat wastewater and convert waste to fuel.....

Sent: Sun 10/23/2011 2:10 PM
Subject: Comment

Solydra story is opening a huge can of worms at the DOE LOAN GURANTEE LOAN PROGRAM. Its not just about the Solar loan guarantee program. Look at all the millions in fees collected by the **DOE LOAN GUARANTEE PROGRAM with projects 20% completion**. Also, an audit needs to be done on DOE GRANTS to individuals from the DOE that are now working in private industry. Very incestuous. There needs to be an audit on each individual loan program for amount funded and results!

The US taxpayer has spent over **$2.5 billion dollars over the last 50 years on algae research**. **To date, nothing has been commercialized by any algae researcher.**

The REAL question is: **Does the DOE BIOMASS PROGRAM really want the US off of foreign oil or do they want to continue funding more grants for algae research to keep algae researchers employed at universities for another 50 years?**

In business, you are not given 50 years to research anything. The problem is in the Congressional Mandate that says the DOE can only use taxpayer monies on algae research, NOT algae production in the US. So far, research has not got the US off of foreign oil for the last 50 years!
anonymous

Fri 10/21/2011 11:03 AM
Re: National Bioeconomy Blueprint

Tom,

It occurred to me that a brief overview of what an Internet pipeline is, does, and how it differs from other Internet applications like search may be helpful. Attached is a brief backgrounder, along with a few slides on how we use a Pipeline as an application example.

Please find attached my 2-page precis for the OST Bioeconomy RFI. If deemed worthwhile, I can provide an expanded version for the RFI.

Regards,

Franco Vitaliano
President & CEO
ExQor Technologies, Inc.

Converging Technologies for Improving Human Performance

NANOTECHNOLOGY, BIOTECHNOLOGY, INFORMATION TECHNOLOGY AND COGNITIVE SCIENCE

NSF/DOC-sponsored report

Edited by Mihail C. Roco and William Sims Bainbridge, National Science Foundation

June 2002

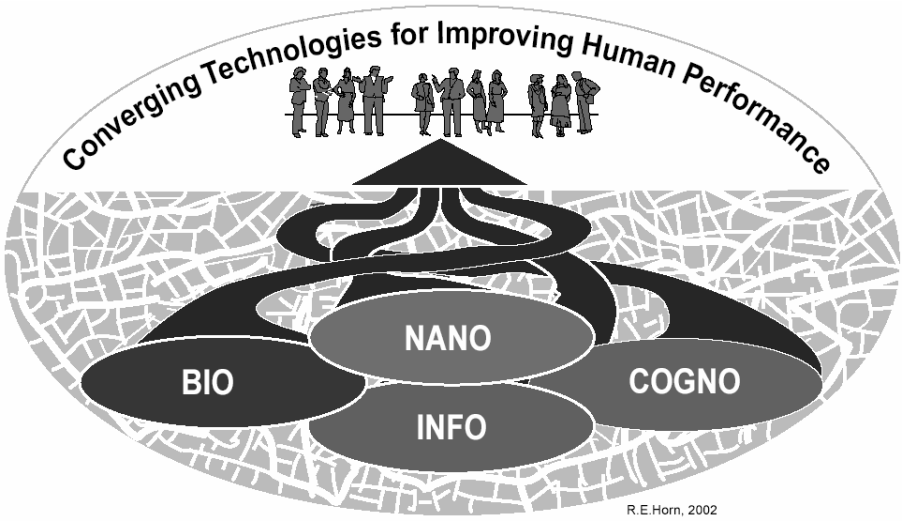
Arlington, Virginia

 This work relates to NSF Grant CTS-0128860, awarded to the World Technology Evaluation Center (WTEC), Inc.

CONVERGING TECHNOLOGIES FOR IMPROVING HUMAN PERFORMANCE:

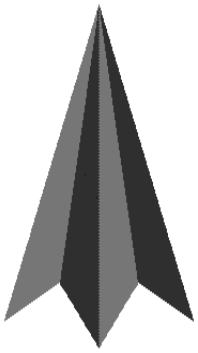
NANOTECHNOLOGY, BIOTECHNOLOGY, INFORMATION TECHNOLOGY AND COGNITIVE SCIENCE

Table of Contents



Changing the societal "fabric" towards a new structure
(upper figure by R.E. Horn)

The integration and synergy of the four technologies (nano-bio-info-cogno) originate from the nanoscale, where the building blocks of matter are established. This picture symbolizes the confluence of technologies that now offers the promise of improving human lives in many ways, and the realignment of traditional disciplinary boundaries that will be needed to realize this potential. New and more direct pathways towards human goals are envisioned in working habits, in economic activity, and in the humanities.



NBIC "arrow"

This picture suggests advancement of converging technologies.

EXECUTIVE SUMMARY

M.C. Roco and W.S. Bainbridge

In the early decades of the 21st century, concentrated efforts can unify science based on the unity of nature, thereby advancing the combination of nanotechnology, biotechnology, information technology, and new technologies based in cognitive science. With proper attention to ethical issues and societal needs, converging technologies could achieve a tremendous improvement in human abilities, societal outcomes, the nation's productivity, and the quality of life. This is a broad, cross-cutting, emerging and timely opportunity of interest to individuals, society and humanity in the long term.

The phrase "convergent technologies" refers to the synergistic combination of four major "NBIC" (nano-bio-info-cogno) provinces of science and technology, each of which is currently progressing at a rapid rate: (a) nanoscience and nanotechnology; (b) biotechnology and biomedicine, including genetic engineering; (c) information technology, including advanced computing and communications; (d) cognitive science, including cognitive neuroscience.

Timely and Broad Opportunity. Convergence of diverse technologies is based on *material unity at the nanoscale and on technology integration from that scale.* The building blocks of matter that are fundamental to all sciences originate at the nanoscale. Revolutionary advances at the interfaces between previously separate fields of science and technology are ready to create key *transforming tools* for NBIC technologies. Developments in systems approaches, mathematics, and computation in conjunction with NBIC allow us for the first time to understand the natural world, human society, and scientific research as *closely coupled complex, hierarchical systems*. At this moment in the evolution of technical achievement, *improvement of human performance through integration of technologies* becomes possible.

Examples of payoffs may include improving work efficiency and learning, enhancing individual sensory and cognitive capabilities, revolutionary changes in healthcare, improving both individual and group creativity, highly effective communication techniques including brain-to-brain interaction, perfecting human-machine interfaces including neuromorphic engineering, sustainable and "intelligent" environments including neuro-ergonomics, enhancing human capabilities for defense purposes, reaching sustainable development using NBIC tools, and ameliorating the physical and cognitive decline that is common to the aging mind.

The workshop participants envision important breakthroughs in NBIC-related areas in the next 10 to 20 years. Fundamental research requires about the same interval to yield significant applications. Now is the time to anticipate the research issues and plan an R&D approach that would yield optimal results.

This report addresses key issues: What are the implications of unifying sciences and converging technologies? How will scientific knowledge and current technologies evolve and what emerging developments are envisioned? What visionary ideas can guide research to accomplish broad benefits for humanity? What are the most pressing research and education issues? How can we develop a transforming national strategy to enhance individual capabilities and overall societal

outcomes? What should be done to achieve the best results over the next 10 to 20 years?

This report underlines several broad, long-term implications of converging technologies in key areas of human activity, including working, learning, aging, group interaction, and human evolution. If we make the correct decisions and investments today, many of these visions could be addressed within 20 years' time. Moving forward simultaneously along many of these paths could achieve an age of innovation and prosperity that would be a turning point in the evolution of human society. The right of each individual to use new knowledge and technologies in order to achieve personal goals, as well as the right to privacy and choice, are at the core of the envisioned developments.

This report is based on exploratory research already initiated in representative research organizations and on the opinions of leading scientists and engineers using research data.

Strategies for Transformation. It is essential to prepare key organizations and societal activities for the changes made possible by converging technologies. Activities that accelerate convergence to improve human performance must be enhanced, including focused research and development, increased technological synergy from the nanoscale, developing of interfaces among sciences and technologies, and a holistic approach to monitor the resultant societal evolution. The aim is to offer individuals and groups an increased range of attractive choices while preserving such fundamental values as privacy, safety, and moral responsibility. Education and training at all levels should use converging science and technology and prepare people to take advantage of them. We must experiment with innovative ideas to motivate multidisciplinary research and development, while finding ways to address ethical, legal, and moral concerns. In many application areas, such as medical technology and healthcare, it is necessary to accelerate advances that would take advantage of converging technologies.

Towards Unifying Science and Converging Technologies. The evolution of a hierarchical architecture for integrating natural and human sciences across many scales, dimensions, and data modalities will be required. Half a millennium ago, Renaissance leaders were masters of several fields simultaneously. Today, however, specialization has splintered the arts and engineering, and no one can master more than a tiny fragment of human creativity. The sciences have reached a watershed at which they must unify if they are to continue to advance rapidly. Convergence of the sciences can initiate a new renaissance, embodying a holistic view of technology based on transformative tools, the mathematics of complex systems, and unified cause-and-effect understanding of the physical world from the nanoscale to the planetary scale.

Major Themes. Scientific leaders and policy makers across a range of fields prepared written statements for a December 2001 workshop, evaluating the potential impact of NBIC technologies on improving human capabilities at the microscopic, individual, group, and societal levels. During the workshop, participants examined the vast potential in six different areas of relevance:

- *Overall potential of converging technologies.* Representatives of government agencies and the private sector set forth the mission to explore the potential of converging technologies and research needs to improve human performance,

as well as the overall potential for revolutionary changes in the economy and society. They identified the synergistic development of nano-, bio-, information- and cognition-based technologies as an outstanding opportunity at the interface and frontier of sciences and engineering in the following decades, and proposed new visions of what is possible to achieve.

- *Expanding human cognition and communication.* Highest priority was given to "The Human Cognome Project," a multidisciplinary effort to understand the structure, functions, and potential enhancement of the human mind. Other priority areas are: personal sensory device interfaces; enriched community through humanized technology; learning how to learn; and enhanced tools for creativity.
- *Improving human health and physical capabilities.* Six priority areas have been identified: nano-bio processors for research and development of treatments, including those resulting from bioinformatics, genomics and proteomics; nanotechnology-based implants and regenerative biosystems as replacements for human organs or for monitoring of physiological well-being; nanoscale machines and comparable unobtrusive tools for medical intervention; multi-modality platforms for increasing sensorial capabilities, particularly for visual and hearing impaired people; brain-to-brain and brain-to-machine interfaces; and virtual environments for training, design, and forms of work unlimited by distance or the physical scale on which it is performed.
- *Enhancing group and societal outcomes.* An NBIC system called "The Communicator" would remove barriers to communication caused by physical disabilities, language differences, geographic distance, and variations in knowledge, thus greatly enhancing the effectiveness of cooperation in schools, corporations, government agencies, and across the world. Other areas of focus are in enhancing group creativity and productivity, cognitive engineering and developments related to networked society. A key priority will be revolutionary new products and services based on the integration of the four technologies from the nanoscale.
- *National security.* Given the radically changing nature of conflict in this new century, seven opportunities to strengthen national defense offered by technological convergence deserve high priority: data linkage and threat anticipation; uninhabited combat vehicles; war fighter education and training; responses to chemical, biological, radiological and explosive threats; war fighter systems; non-drug treatments to enhance human performance; and applications of human-machine interfaces.
- *Unifying science and education.* To meet the coming challenges, scientific education needs radical transformation from elementary school through post-graduate training. Convergence of previously separate scientific disciplines and fields of engineering cannot take place without the emergence of new kinds of people who understand multiple fields in depth and can intelligently work to integrate them. New curricula, new concepts to provide intellectual coherence, and new forms of educational institutions will be necessary.

Beyond the 20-year time span, or outside the current boundaries of high technology, convergence can have significant impacts in such areas as: work efficiency, the human body and mind throughout the life cycle, communication and education, mental health, aeronautics and space flight, food and farming, sustainable and intelligent environments, self-presentation and fashion, and transformation of civilization.

Synopsis of Recommendations

The recommendations of this report are far-reaching and fundamental, urging the transformation of science, engineering and technology at their very roots. The new developments will be revolutionary and must be governed by respect for human welfare and dignity. This report sets goals for societal and educational transformation. Building on the suggestions developed in the five topical groups, and the ideas in the more than 50 individual contributions, the workshop recommended a **national R&D priority area on converging technologies focused on enhancing human performance.** The opportunity is broad, enduring, and of general interest.

a) **Individuals.** Scientists and engineers at every career level should gain skills in at least one NBIC area and in neighboring disciplines, collaborate with colleagues in other fields, and take risks in launching innovative projects that could advance NBIC.

b) **Academe.** Educational institutions at all levels should undertake major curricular and organizational reforms to restructure the teaching and research of science and engineering so that previously separate disciplines can converge around common principles to train the technical labor force for the future.

c) **Private Sector.** Manufacturing, biotechnology, information and medical service corporations will need to develop partnerships of unparalleled scope to exploit the tremendous opportunities from technological convergence, investing in production facilities based on entirely new principles, materials, devices and systems, with increased emphasis on human development.

d) **Government.** The Federal Government should establish a national research and development priority area on converging technologies focused on enhancing human performance. Government organizations at all levels should provide leadership in creating the NBIC infrastructure and coordinating the work of other institutions, and must accelerate convergence by supporting new multidisciplinary scientific efforts while sustaining the traditional disciplines that are essential for success. Ethical, legal, moral, economic, environmental, workforce development, and other societal implications must be addressed from the beginning, involving leading NBIC scientists and engineers, social scientists and a broad coalition of professional and civic organizations. Research on societal implications must be funded, and the risk of potential undesirable secondary effects must be monitored by a government organization in order to anticipate and take corrective action. Tools should be developed to anticipate scenarios for future technology development and applications.

e) **Professional Societies.** The scientific and engineering communities should create new means of interdisciplinary training and communication, reduce the barriers that inhibit individuals from working across disciplines, aggressively highlight opportunities for convergence in their conferences, develop links to a variety of other technical and medical organizations, and address ethical issues related to technological developments.

f) **Other Organizations.** Non-governmental organizations that represent potential user groups should contribute to the design and testing of convergent technologies, in order to maximize the benefits for their diverse constituencies. Private research foundations should invest in NBIC research in those areas that are consistent with their unique missions. The press should increase high-quality coverage of science and technology, on the basis of the new convergent paradigm, to inform citizens so they can participate wisely in debates about ethical issues such as unexpected effects on inequality, policies concerning diversity, and the implications of transforming human capabilities.

A vast opportunity is created by the convergence of sciences and technologies starting with integration from the nanoscale and having immense individual, societal and historical implications for human development. The participants in the meetings who prepared this report recommend *a national research and development priority area on converging technologies focused on enhancing human performance*. This would be a suitable framework for a long-term, coherent strategy in research and education. Science and technology will increasingly dominate the world, as population, resource exploitation, and potential social conflict grow. Therefore, the success of this convergent technologies priority area is essential to the future of humanity.

OVERVIEW
CONVERGING TECHNOLOGIES FOR IMPROVING HUMAN PERFORMANCE:

Nanotechnology, Biotechnology, Information Technology, and Cognitive Science (NBIC)

M.C. Roco and W.S. Bainbridge

1. Background

We stand at the threshold of a new renaissance in science and technology, based on a comprehensive understanding of the structure and behavior of matter from the nanoscale up to the most complex system yet discovered, the human brain. Unification of science based on unity in nature and its holistic investigation will lead to technological convergence and a more efficient societal structure for reaching human goals. In the early decades of the twenty-first century, concentrated effort can bring together nanotechnology, biotechnology, information technology, and new technologies based in cognitive science. With proper attention to ethical issues and societal needs, the result can be a tremendous improvement in human abilities, new industries and products, societal outcomes, and quality of life.

Rapid advances in convergent technologies have the potential to enhance both human performance and the nation's productivity. Examples of payoffs will include improving work efficiency and learning, enhancing individual sensory and cognitive capabilities, fundamentally new manufacturing processes and improved products, revolutionary changes in healthcare, improving both individual and group efficiency, highly effective communication techniques including brain-to-brain interaction, perfecting human-machine interfaces including neuromorphic engineering for industrial and personal use, enhancing human capabilities for defense purposes, reaching sustainable development using NBIC tools, and ameliorating the physical and cognitive decline that is common to the aging mind.

This report addresses several main issues: What are the implications of unifying sciences and converging technologies? How will scientific knowledge and current technologies evolve and what emerging developments are envisioned? What should be done to achieve the best results over the next 10 to 20 years? What visionary ideas can guide research to accomplish broad benefits for humanity? What are the most pressing research and education issues? How can we develop a transforming national strategy to enhance individual capabilities and overall societal outcomes? These issues were discussed on December 3-4, 2001, at the workshop on Converging Technologies to Improve Human Performance, and in contributions submitted after that meeting for this report.

The phrase "convergent technologies" refers to the synergistic combination of four major "NBIC" (nano-bio-info-cogno) provinces of science and technology, each of which is currently progressing at a rapid rate: (a) nanoscience and nanotechnology; (b) biotechnology and biomedicine, including genetic engineering;

(c) information technology, including advanced computing and communications; and (d) cognitive science, including cognitive neuroscience.

This report is based on exploratory research already initiated in representative research organizations and on the opinions of leading scientists and engineers using research data. Contributors to this report have considered possibilities for progress based on full awareness of ethical as well as scientific principles.

Accelerated scientific and social progress can be achieved by combining research methods and results across these provinces in duos, trios, and the full quartet. Figure 1 shows the "NBIC tetrahedron," which symbolizes this convergence. Each field is represented by a vertex, each pair of fields by a line, each set of three fields by a surface, and the entire union of all four fields by the volume of the tetrahedron.

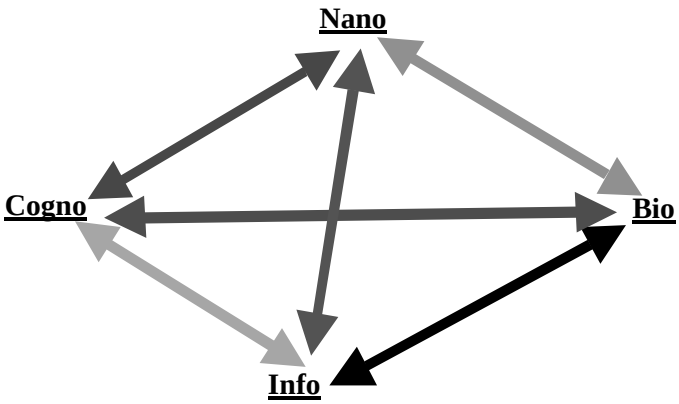


Figure 1. NBIC tetrahedron.

2. Timely and Broad Opportunity

The sciences have reached a watershed at which they must combine in order to advance most rapidly. The new renaissance must be based on a holistic view of science and technology that envisions new technical possibilities and focuses on people. The unification of science and technology can yield results over the next two decades on the basis of four key principles: material unity at the nanoscale, NBIC transforming tools, hierarchical systems, and improvement of human performance, as described below:

a) Convergence of diverse technologies is based on *material unity at the nanoscale and on technology integration from that scale*. Science can now understand the ways in which atoms combine to form complex molecules, and how these in turn aggregate according to common fundamental principles to form both organic and inorganic structures. Technology can harness natural processes to engineer new materials, biological products, and machines from the nanoscale up to the scale of meters. The same principles will allow us to understand and, when desirable, to control the behavior both of complex microsystems, such as neurons and computer components, and macrosystems, such as human metabolism and transportation vehicles.

b) Revolutionary advances at the interfaces between previously separate fields of science and technology are ready to create key *NBIC transforming tools (nano-, bio, info-, and cognitive-based technologies)*, including scientific instruments, analytical methodologies, and radically new materials systems. The innovative momentum in these interdisciplinary areas must not be lost but harnessed to accelerate unification of the disciplines. Progress can become self-catalyzing if we press forward aggressively; but if we hesitate, the barriers to progress may crystallize and become harder to surmount.

c) Developments in systems approaches, mathematics, and computation in conjunction with work in NBIC areas allow us for the first time to understand the natural world and cognition in terms of *complex, hierarchical systems*. Applied both to particular research problems and to the overall organization of the research enterprise, this complex systems approach provides holistic awareness of opportunities for integration, in order to obtain maximum synergy along the main directions of progress.

d) At this unique moment in the history of technical achievement, *improvement of human performance* becomes possible. Caught in the grip of social, political, and economic conflicts, the world hovers between optimism and pessimism. NBIC convergence can give us the means to deal successfully with these challenges by substantially enhancing human mental, physical, and social abilities. Better understanding of the human body and development of tools for direct human-machine interaction have opened completely new opportunities. Efforts must center on individual and collective human advancement, in terms of an enlightened conception of human benefit that embraces change while preserving fundamental values.

The history of science across the vast sweep of human history undermines any complacency that progress will somehow happen automatically, without the necessity for vigorous action. Most societies at most points in their history were uninterested in science, and they advanced technologically only very slowly, if at all. On rare occasions, such as the pyramid-building age in ancient Egypt or the roughly contemporaneous emergence of intensive agriculture and trade in Babylon, the speed of progress seemed to accelerate, although at a much slower rate than that experienced by Europe and North America over the past five centuries. For modern civilization, the most relevant and instructive precursor remains the classical civilizations of Greece and Rome. Building on the scientific accomplishments of the Babylonians and Egyptians, the Greeks accomplished much in mathematics, astronomy, biology, and other sciences. Their technological achievements probably peaked in the Hellenistic Age as city-states gave way to larger political units, culminating in Roman dominance of the entire Mediterranean area. By the end of the second century, if not long before, scientific and technological progress had slowed with the fall of Rome. Historians debate the degree to which technology advanced during the subsequent Dark Ages and Medieval Period, but clearly, a mighty civilization had fallen into bloody chaos and widespread ignorance.

The Renaissance, coming a thousand years after the decline and fall of the Roman Empire, reestablished science on a stronger basis than before, and technological advancement has continued on an accelerating path since then. The

hallmark of the Renaissance was its holistic quality, as all fields of art, engineering, science, and culture shared the same exciting spirit and many of the same intellectual principles. A creative individual, schooled in multiple arts, might be a painter one day, an engineer the next, and a writer the day after that. However, as the centuries passed, the holism of the Renaissance gave way to specialization and intellectual fragmentation. Today, with the scientific work of recent decades showing us at a deeper level the fundamental unity of natural organization, it is time to rekindle the spirit of the Renaissance, returning to the holistic perspective on a higher level, with a new set of principles and theories. This report underlines several broad, long-term implications of converging technologies in key areas of human activity:

- Societal productivity, in terms of well-being as well as economic growth
- Security from natural and human-generated disasters
- Individual and group performance and communication
- Life-long learning, graceful aging, and a healthy life
- Coherent technological developments and their integration with human activities
- Human evolution, including individual and cultural evolution

Fundamental scientific discovery needs at least ten years to be implemented in new technologies, industries, and ways of life. Thus, if we want the great benefits of NBIC convergence within our own lifetimes, now is the right time to begin. The impact of advancing technology on the present quality of life (United Nations Development Program 2001) will be accelerated by NBIC, and new possibilities for human performance will be unleashed.

3. Vision for Enhancing Human Abilities and Societal Performance

Despite moments of insight and even genius, the human mind often seems to fall far below its full potential. The level of human thought varies greatly in awareness, efficiency, creativity, and accuracy. Our physical and sensory capabilities are limited and susceptible to rapid deterioration in accidents or disease and gradual degradation through aging (Stern and Carstensen 2000). All too often we communicate poorly with each other, and groups fail to achieve their desired goals. Our tools are difficult to handle, rather than being natural extensions of our capabilities. In the coming decades, however, converging technologies promise to increase significantly our level of understanding, transform human sensory and physical capabilities, and improve interactions between mind and tool, individual and team. This report addresses key issues concerning how to reach these goals.

Each scientific and engineering field has much to contribute to enhancing human abilities, to solving the pressing problems faced by our society in the twenty-first century, and to expanding human knowledge about our species and the world we inhabit; but combined, their potential contribution is vast. Following are twenty ways the workshop determined that convergent technologies could benefit humanity in a time frame of 10 to 20 years. Each of these scenarios are presented in detail in the body of the report:

- Fast, broadband interfaces directly between the human brain and machines will transform work in factories, control automobiles, ensure military superiority, and enable new sports, art forms and modes of interaction between people.
- Comfortable, wearable sensors and computers will enhance every person's awareness of his or her health condition, environment, chemical pollutants, potential hazards, and information of interest about local businesses, natural resources, and the like.
- Robots and software agents will be far more useful for human beings, because they will operate on principles compatible with human goals, awareness, and personality.
- People from all backgrounds and of all ranges of ability will learn valuable new knowledge and skills more reliably and quickly, whether in school, on the job, or at home.
- Individuals and teams will be able to communicate and cooperate profitably across traditional barriers of culture, language, distance, and professional specialization, thus greatly increasing the effectiveness of groups, organizations, and multinational partnerships.
- The human body will be more durable, healthier, more energetic, easier to repair, and more resistant to many kinds of stress, biological threats, and aging processes.
- Machines and structures of all kinds, from homes to aircraft, will be constructed of materials that have exactly the desired properties, including the ability to adapt to changing situations, high energy efficiency, and environmental friendliness.
- A combination of technologies and treatments will compensate for many physical and mental disabilities and will eradicate altogether some handicaps that have plagued the lives of millions of people.
- National security will be greatly strengthened by lightweight, information-rich war fighting systems, capable uninhabited combat vehicles, adaptable smart materials, invulnerable data networks, superior intelligence-gathering systems, and effective measures against biological, chemical, radiological, and nuclear attacks.
- Anywhere in the world, an individual will have instantaneous access to needed information, whether practical or scientific in nature, in a form tailored for most effective use by the particular individual.
- Engineers, artists, architects, and designers will experience tremendously expanded creative abilities, both with a variety of new tools and through improved understanding of the wellsprings of human creativity.
- The ability to control the genetics of humans, animals, and agricultural plants will greatly benefit human welfare; widespread consensus about ethical, legal, and moral issues will be built in the process.

- The vast promise of outer space will finally be realized by means of efficient launch vehicles, robotic construction of extraterrestrial bases, and profitable exploitation of the resources of the Moon, Mars, or near-Earth approaching asteroids.
- New organizational structures and management principles based on fast, reliable communication of needed information will vastly increase the effectiveness of administrators in business, education, and government.
- Average persons, as well as policymakers, will have a vastly improved awareness of the cognitive, social, and biological forces operating their lives, enabling far better adjustment, creativity, and daily decision making.
- Factories of tomorrow will be organized around converging technologies and increased human-machine capabilities as "intelligent environments" that achieve the maximum benefits of both mass production and custom design.
- Agriculture and the food industry will greatly increase yields and reduce spoilage through networks of cheap, smart sensors that constantly monitor the condition and needs of plants, animals, and farm products.
- Transportation will be safe, cheap, and fast, due to ubiquitous realtime information systems, extremely high-efficiency vehicle designs, and the use of synthetic materials and machines fabricated from the nanoscale for optimum performance.
- The work of scientists will be revolutionized by importing approaches pioneered in other sciences, for example, genetic research employing principles from natural language processing and cultural research employing principles from genetics.
- Formal education will be transformed by a unified but diverse curriculum based on a comprehensive, hierarchical intellectual paradigm for understanding the architecture of the physical world from the nanoscale through the cosmic scale.

If we make the correct decisions and investments today, any of these visions could be achieved within 20 years' time. Moving forward simultaneously along many of these paths could achieve a golden age that would be a turning point for human productivity and quality of life. Technological convergence could become the framework for human convergence (Ostrum et al. 2002). The twenty-first century could end in world peace, universal prosperity, and evolution to a higher level of compassion and accomplishment. It is hard to find the right metaphor to see a century into the future, but it may be that humanity would become like a single, distributed and interconnected "brain" based in new core pathways of society. This will be an enhancement to the productivity and independence of individuals, giving them greater opportunities to achieve personal goals.

Table 1 shows a simplified framework for classifying improving human performance areas as they relate to an individual (see also Spohrer 2002, in this volume).

Table 1. Main improvement areas relative to an individual

Relative position	Improvement area
External (outside the body), environmental	• New products: materials, devices and systems, agriculture and food • New agents: societal changes, organizations, robots, chat-bots, animals • New mediators: stationary tools and artifacts • New places: real, virtual, mixed
External, collective	• Enhanced group interaction and creativity • Unifying science education and learning
External, personal	• New mediators: mobile/wearable tools and artifacts
Internal (inside the body), temporary	• New ingestible medicines, food
Internal, permanent	• New organs: new sensors and effectors, implantables • New skills: converging technologies, new uses of old sensors and effectors • New genes: new genetics, cells

4. Strategies for Transformation

Science and engineering as well as societal activities are expected to change, regardless of whether there are policies to guide or promote such changes. To influence and accelerate changes in the most beneficial directions, it is not enough to wait patiently while scientists and engineers do their traditional work. Rather, the full advantages of NBIC developments may be achieved by making special efforts to break down barriers between fields and to develop the new intellectual and

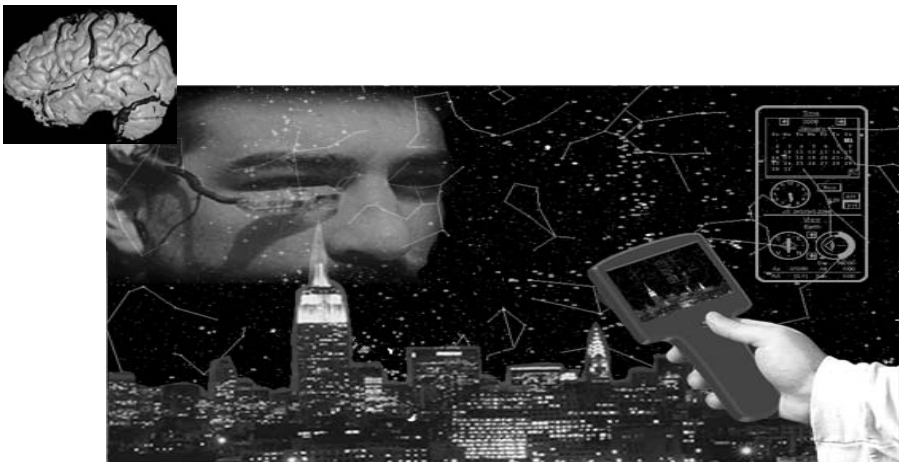


Figure 2. Vision of the world as a distributed, interconnected "brain" with various architectural levels that can empower individuals with access to collective knowledge while safeguarding privacy.

physical resources that are needed. The workshop identified the following general strategies for achieving convergence:

a) We should prepare key organizations and social activities for the envisioned changes made possible by converging technologies. This requires establishing long-term goals for major organizations and modeling them to be most effective in the new setting.

b) Activities must be enhanced that accelerate convergence of technologies for improving human performance, including focused research, development, and design; increasing synergy from the nanoscale; developing interfaces among sciences and technologies; and taking a holistic approach to monitor the resultant societal evolution. The aim is to offer individuals and groups an increased range of attractive choices while preserving fundamental values such as privacy, safety, and moral responsibility. A research and development program for exploring the long-term potential is needed.

c) Education and training at all levels should use converging technologies as well as prepare people to take advantage of them. Interdisciplinary education programs, especially in graduate school, can create a new generation of scientists and engineers who are comfortable working across fields and collaborating with colleagues from a variety of specialties. Essential to this effort is the integration of research and education that combines theoretical training with experience gained in the laboratory, industry, and world of application. A sterling example is NSF's competition called Integrative Graduate Education and Research Training (IGERT). A number of comparable graduate education projects need to be launched at the intersections of crucial fields to build a scientific community that will achieve the convergence of technologies that can greatly improve human capabilities.

d) Experimentation with innovative ideas is needed to focus and motivate needed multidisciplinary developments. For example, there could be a high-visibility annual event, comparable to the sports Olympics, between information technology interface systems that would compete in terms of speed, accuracy, and other measurements of enhanced human performance. Professional societies could set performance targets and establish criteria for measuring progress toward them.

e) Concentrated multidisciplinary research thrusts could achieve crucially important results. Among the most promising of such proposed endeavors are the Human Cognome Project to understand the nature of the human mind, the development of a "Communicator" system to optimize human teams and organizations, and the drive to enhance human physiology and physical performance. Such efforts probably require the establishment of networks of research centers dedicated to each goal, funded by coalitions of government agencies and operated by consortia of universities and corporations.

f) Flourishing communities of NBIC scientists and engineers will need a variety of multiuser, multiuse research and information facilities. Among these will be data infrastructure archives, that employ advanced digital technology to serve a wide range of clients, including government agencies, industrial designers, and university laboratories. Other indispensable facilities would

include regional nanoscience centers, shared brain scan resources, and engineering simulation supercomputers. Science is only as good as its instrumentation, and information is an essential tool of engineering, so cutting-edge infrastructure must be created in each area where we desire rapid progress.

g) Integration of the sciences will require establishment of a shared culture that spans across existing fields. Interdisciplinary journals, periodic new conferences, and formal partnerships between professional organizations must be established. A new technical language will need to be developed for communicating the unprecedented scientific and engineering challenges based in the mathematics of complex systems, the physics of structures at the nanoscale, and the hierarchical logic of intelligence.

h) We must find ways to address ethical, legal, and moral concerns, throughout the process of research, development, and deployment of convergent technologies. This will require new mechanisms to ensure representation of the public interest in all major NBIC projects, to incorporate ethical and social-scientific education in the training of scientists and engineers, and to ensure that policy makers are thoroughly aware of the scientific and engineering implications of the issues they face. Examples are the moral and ethical issues involved in applying new brain-related scientific findings (*Brain Work* 2002). Should we make our own ethical decisions or "are there things we'd rather not know" (Kennedy 2002)? To live in harmony with nature, we must understand natural processes and be prepared to protect or harness them as required for human welfare. Technological convergence may be the best hope for the preservation of the natural environment, because it integrates humanity with nature across the widest range of endeavors, based on systematic knowledge for wise stewardship of the planet.

i) It is necessary to accelerate developments in medical technology and healthcare in order to obtain maximum benefit from converging technologies, including molecular medicine and nano-engineered medication delivery systems, assistive devices to alleviate mental and emotional disabilities, rapid sensing and preventive measures to block the spread of infectious and environmental diseases, continuous detection and correction of abnormal individual health indications, and integration of genetic therapy and genome-aware treatment into daily medical practice. To accomplish this, research laboratories, pharmaceutical companies, hospitals and health maintenance organizations, and medical schools will need to expand greatly their institutional partnerships and technical scope.

General Comments

There should be specific partnerships among high-technology agencies and university researchers in such areas as space flight, where a good foundation for cutting edge technological convergence already exists. But in a range of other areas, it will be necessary to build scientific communities and research projects nearly from scratch. It could be important to launch a small number of well-financed and well-designed demonstration projects to promote technological convergence in a variety of currently low-technology areas.

The U.S. economy has benefited greatly from the rapid development of advanced technology, both through increased international competitiveness and through growth in new industries. Convergent technologies could transform some low-technology fields into high-technology fields, thereby increasing the fraction of the U.S. economy that is both growing and world-preeminent.

This beneficial transformation will not take place without fundamental research in fields where such research has tended to be rare or without the intensity of imagination and entrepreneurship that can create new products, services, and entire new industries. We must begin with a far-sighted vision that a renaissance in science and technology can be achieved through the convergence of nanotechnology, biotechnology, information technology, and cognitive science.

5. Towards Unifying Science and Converging Technology

Although recent progress in the four NBIC realms has been remarkable, further rapid progress in many areas will not happen automatically. Indeed, science and engineering have encountered several barriers, and others are likely to appear as we press forward. In other areas, progress has been hard-won, and anything that could accelerate discovery would be exceedingly valuable. For example, cognitive neuroscience has made great strides recently unlocking the secrets of the human brain, with such computer-assisted techniques as functional magnetic resonance imaging (fMRI). However, current methods already use the maximum magnetic field strength that is considered safe for human beings. The smallest structures in the brain that can routinely be imaged with this technique are about a cubic millimeter in size, but this volume can contain tens of thousands of neurons, so it really does not let scientists see many of the most important structures that are closer to the cellular level. To increase the resolution further will require a new approach, whether novel computer techniques to extract more information from fMRI data or a wholly different method to study the structure and function of regions of the brain, perhaps based on a marriage of biology and nanotechnology.

Another example is in the area of information science, where progress has depended largely upon the constant improvement in the speed and cost-effectiveness of integrated circuits. However, current methods are nearing their physical limits, and it is widely believed that progress will cease in a few years unless new approaches are found. Nanotechnology offers realistic hope that it will be possible to continue the improvement in hardware for a decade or even two decades longer than current methods will permit. Opinion varies on how rapidly software capabilities are improving at the present time, but clearly, software efficiency has not improved at anything like the rate of hardware, so any breakthrough that increases the rate of software progress would be especially welcome. One very promising direction to look for innovations is biocomputing, a host of software methods that employ metaphors from such branches of biology as genetics. Another is cognitive science, which can help computer scientists develop software inspired by growing understanding of the neural architectures and algorithms actually employed by the human brain.

Many other cases could be cited in which discoveries or inventions in one area will permit progress in others. Without advances in information technology, we cannot take full advantage of biotechnology in areas such as decoding the human

genome, modeling the dynamic structure of protein molecules, and understanding how genetically engineered crops will interact with the natural environment. Information technology and microbiology can provide tools for assembling nanoscale structures and incorporating them effectively in microscale devices. Convergence of nonorganic nanoscience and biology will require breakthroughs in the ways we conceptualize and teach the fundamental processes of chemistry in complex systems, which could be greatly facilitated by cognitive science research on scientific thinking itself.

Thus, in order to attain the maximum benefit from scientific progress, the goal can be nothing less than a fundamental transformation of science and engineering. Although the lists of potential medium-term benefits have naturally stressed applications, much of the unification must take place on the level of fundamental science. From empirical research, theoretical analysis, and computer modeling we will have to develop overarching scientific principles that unite fields and make it possible for scientists to understand complex phenomena. One of the reasons sciences have not merged in the past is that their subject matter is so complex and challenging to the human intellect. We must find ways to rearrange and connect scientific findings so that scientists from a wider range of fields can comprehend and apply them within their own work. It will therefore be necessary to support fundamental scientific research in each field that can become the foundation of a bridge to other fields, as well as support fundamental research at the intersections of fields.

Fundamental research will also be essential in engineering, including computer engineering, because engineers must be ready in the future to take on entirely new tasks from those they have traditionally handled. The traditional tool kit of engineering methods will be of limited utility in some of the most important areas of technological convergence, so new tools will have to be created. This has already begun to happen in nanotechnology, but much work remains to be done developing engineering solutions to the problems raised by biology, information, and the human mind.

It is possible to identify a number of areas for fundamental scientific research that will have especially great significance over the coming twenty years for technological convergence to improve human performance. Among these, the following four areas illustrate how progress in one of the NBIC fields can be energized by input from others:

- *Entirely new categories of materials, devices, and systems for use in manufacturing, construction, transportation, medicine, emerging technologies, and scientific research.* Nanotechnology is obviously preeminent here, but information technology plays a crucial role in both research and design of the structure and properties of materials and in the design of complex molecular and microscale structures. It has been pointed out that industries of the future will use engineered biological processes to manufacture valuable new materials, but it is also true that fundamental knowledge about the molecular-level processes essential to the growth and metabolism of living cells may be applied, through analogy, to development of new inorganic materials. Fundamental materials science research in mathematics, physics, chemistry, and biology will be essential.

- *The living cell, which is the most complex known form of matter with a system of components and processes operating at the nanoscale.* The basic properties and functions are established at the first level of organization of biosystems, that is, at the nanoscale. Recent work at the intersection of biotechnology and microelectronics, notably the so-called gene-on-a-chip approach, suggests that a union of nanotechnology, biotechnology, and computer science may be able to create "bio-nano processors" for programming complex biological pathways that will mimic cellular processes on a chip. Other research methodologies may come from the ongoing work to understand how genes are expressed in the living body as physical structures and chemical activities. Virtual reality and augmented reality computer technology will allow scientists to visualize the cell from inside, as it were, and to see exactly what they are doing as they manipulate individual protein molecules and cellular nanostructures.
- *Fundamental principles of advanced sensory, computational, and communications systems, especially the integration of diverse components into the ubiquitous and global network.* Breakthroughs in nanotechnology will be necessary to sustain the rapid improvement of computer hardware over the next 20 years. From biology will come important insights about the behavior of complex dynamic systems and specific methods of sensing organic and chemical agents in the environment. Cognitive science will provide insights into ways to present information to human beings so they can use it most effectively. A particularly challenging set of problems confronting computer and information science and engineering at the present time is how to achieve reliability and security in a ubiquitous network that collects and offers diverse kinds of information in multiple modalities, everywhere and instantly at any moment.
- *The structure, function, and occasional dysfunction of intelligent systems, most importantly, the human mind.* Biotechnology, nanotechnology, and computer simulations can offer powerful new techniques for studying the dynamic behavior of the brain, from the receptors and other structures far smaller than a single neuron, up through individual neurons, functionally specific modules composed of many neurons, the major components of the brain, and then the entire brain as a complex but unified system. Cognition cannot be understood without attention also to the interaction of the individual with the environment, including the ambient culture. Information technology will be crucial in processing data about the brain, notably the difficult challenge of understanding the mature human brain as a product of genetics and development. But it will also be essential to experiment with artificial intelligent systems, such as neural networks, genetic algorithms, autonomous agents, logic-based learning programs, and sophisticated information storage and retrieval systems.

The complementarity of the four NBIC areas is suggested by the statement of workshop participant W.A. Wallace:

If the *Cognitive Scientists* can think it
the *Nano* people can build it
the *Bio* people can implement it, and
the *IT* people can monitor and control it

Each of the four research challenges described above focuses on one of the NBIC areas (nanotechnology, biotechnology, information technology, and cognitive science) and shows how progress can be catalyzed by convergence with the other areas. They are not merely convenient didactic examples, but represent fascinating questions, the answers to which would enable significant improvements in human performance. However, convergence will be possible only if we overcome substantial intellectual barriers.

Especially demanding will be the development of a hierarchical architecture for integrating sciences across many scales, dimensions, and data modalities. For a century or more, educated people have understood that knowledge can be organized in a hierarchy of sciences, from physics as a base, up through chemistry and biology, to psychology and economics. But only now is it really possible to see in detail how each level of phenomena both rests upon and informs the one below. Some partisans for independence of biology, psychology, and the social sciences have argued against "reductionism," asserting that their fields had discovered autonomous truths that should not be reduced to the laws of other sciences. But such a discipline-centric outlook is self-defeating, because as this report makes clear, through recognizing their connections with each other, all the sciences can progress more effectively. A trend towards unifying knowledge by combining natural sciences, social sciences, and humanities using cause-and-effect explanation has already begun (NYAS 2002), and it should be reflected in the coherence of science and engineering trends (Roco 2002, in this report) and in the integration of R&D funding programs.

The architecture of the sciences will be built through understanding of the architecture of nature. At the nanoscale, atoms and simple molecules connect into complex structures like DNA, the subsystems of the living cell, or the next generation of microelectronic components. At the microscale, cells such as the neurons and glia of the human brain interact to produce the transcendent phenomena of memory, emotion, and thought itself. At the scale of the human body, the myriad processes of chemistry, physiology, and cognition unite to form life, action, and individuals capable of creating and benefiting from technology.

Half a millennium ago, Renaissance artist-engineers like Leonardo da Vinci, Filippo Brunelleschi, and Benvenuto Cellini were masters of several fields simultaneously. Today, however, specialization has splintered the arts and engineering, and no one can master more than a tiny fragment of human creativity. We envision that convergence of the sciences can initiate a new renaissance, embodying a holistic view of technology based on transformative tools, the mathematics of complex systems, and unified understanding of the physical world from the nanoscale to the planetary scale.

6. Major Themes

A planning meeting was held May 11, 2001, at the National Science Foundation to develop the agenda for the December workshop and to identify key participants

from academia, industry, and government. Scientific leaders and policymakers across a range of fields were asked to prepare formal speeches for plenary sessions, and all participants were invited to contribute written statements evaluating the potential impact of NBIC technologies on improving human capabilities at the microscopic, individual, group, and societal levels.

Participants in the December 2001 workshop on Convergent Technologies to Improve Human Performance submitted more than fifty written contributions, each of which is like a single piece in a jigsaw puzzle. Together, they depict the future unification of nanotechnology, biotechnology, information technology, and cognitive science, with the amazing benefits these promise. Roughly half of these written contributions, which we call *statements*, describe the current situation and suggest strategies for building upon it. The other half describe *visions* of what could be accomplished in 10 or 20 years. During the workshop, participants examined the vast potential of NBIC in five different areas of relevance, as well as the overall potential for changing the economy, society, and research needs:

a) Overall Potential of Converging Technologies. In plenary sessions of the workshop, representatives of government agencies and the private sector set forth the mission to explore the potential of converging technologies to improve human performance. They identified the synergistic development of nano-, bio-, information- and cognition-based technologies as the outstanding opportunity at the interface and frontier of sciences in the following decades. They proclaimed that it is essential to courageously identify new technologies that have great potential, to develop transforming visions for them, and to launch new partnerships between government agencies, industry, and educational institutions to achieve this potential. Government has an important role in setting long-term research priorities, respecting the ethical and social aspects of potential uses of technology, and ensuring economic conditions that facilitate the rapid invention and deployment of beneficial technologies. Technological superiority is the fundamental basis of the economic prosperity and national security of the United States, and continued progress in NBIC technologies is an essential component for government agencies to accomplish their designated missions. Science and engineering must offer society new visions of what it is possible to achieve through interdisciplinary research projects designed to promote technological convergence.

b) Expanding Human Cognition and Communication. This group of workshop participants examined needs and opportunities in the areas of human cognitive and perceptual functions, communication between individuals and machines programmed with human-like characteristics, and the ways that convergent technologies could enhance our understanding and effective use of human mental abilities. The group identified five areas where accelerated efforts to achieve technological convergence would be especially worthwhile. Highest priority was given to what Robert Horn called The Human Cognome Project, a proposed multidisciplinary effort to understand the structure, functions, and potential enhancement of the human mind. The four other priority areas were personal sensory device interfaces, enriched community through humanized technology, learning how to learn, and enhanced tools for creativity.

c) Improving Human Health and Physical Capabilities. This group of workshop participants also focused primarily on the individual, but on his or her physical rather than mental abilities. Essential to progress in this area is comprehensive scientific understanding of the fundamental chemical and biological processes of life. Control of metabolism in cells, tissue, organs, and organisms is sought. Direct conversion of bio-molecular signals and useful neural codes to man-made motors will open opportunities to direct brain control of devices via neuromorphic engineering. Six technological capabilities for improvement of human health and physical performance received high priority: bio-nano machines for development of treatments, including those resulting from bioinformatics, genomics and proteomics; nanotechnology-based implants as replacements for human organs (Lavine et al. 2002) or for monitoring of physiological well-being; nanoscale robots and comparable unobtrusive tools for medical intervention; extending brain-to-brain and brain-to-machine interfaces using connections to the human neural system; multi-modality platforms for vision- and hearing-impaired people; and virtual environments for training, design, and forms of work unlimited by distance or the physical scale on which it is performed.

d) Enhancing Group and Societal Outcomes. This group of workshop participants examined the implications of technological convergence for human social behavior, social cognition, interpersonal relations, group processes, the use of language, learning in formal and informal settings, and the psychophysiological correlates of social behavior. A wide range of likely benefits to communities and the nation as a whole has been identified, and a specific vision has been proposed of how these benefits could be achieved through a focused research effort to develop a system this group called The Communicator. This NBIC technology would remove barriers to communication caused by disabilities, language differences, geographic distance, and variations in knowledge, thus greatly enhancing the effectiveness of cooperation in schools, in corporations, in government agencies, and across the world. Converging technologies will lead to revolutionary new industries, products and services based on the synergism and integration of biology, information, and cognitive sciences from the nanoscale.

e) National Security. This group of workshop participants examined the radically changing nature of conflict in this new century and the opportunities to strengthen national defense offered by technological convergence. It identified seven highly diverse goals: data linkage and threat anticipation; uninhabited combat vehicles; war fighter education and training; responses to chemical, biological, radiological, and explosive threats; war fighter systems; non-drug treatments to enhance human performance; exoskeletons for physical performance augmentation; preventing brain changes caused by sleep deprivation; and applications of brain-machine interfaces. These highly varied goals could be achieved through specific convergences of NBIC technologies.

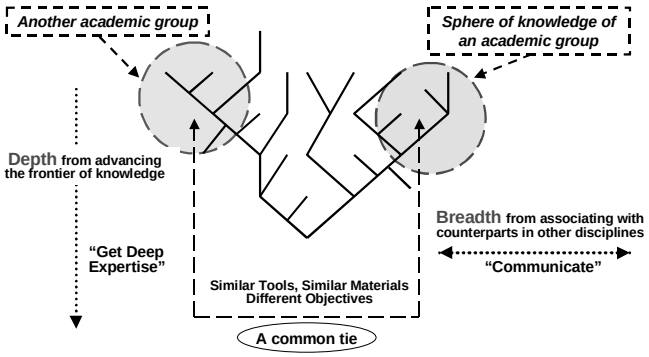


Figure 3. Combining depth with breath in NBIC education and research of various groups.

f) Unifying Science and Education. The final group examined the opportunities for unifying science and the current limitations of scientific education, which is poorly designed to meet the coming challenges. The group documented the need for radical transformation in science education from elementary school through postgraduate training. Part of the answer will come from the convergence of NBIC technologies themselves, which will offer valuable new tools and modalities for education. But convergence of previously separate scientific disciplines and fields of engineering cannot take place without the emergence of new kinds of personnel who understand multiple fields in depth and can intelligently work to integrate them (Figure 3; see Tolles 2002, in this volume). New curricula, new concepts to provide intellectual coherence, and new types of educational institutions will be necessary.

Thus, based on the contributions of individual participants and the work of the six subgroups, the workshop identified the major areas where improved human performance is needed, and identified both short-term and longer-term opportunities to apply convergent technologies to these needs. Table 2 summarizes the key visionary projects discussed in this report. Progress was made in developing a transforming management plan for what should be done to integrate the sciences and engineering in accordance with the convergent technologies vision, including advice to government policymakers. In addition, the workshop recognized specific needs to develop meaningful partnerships and coherent interdisciplinary activities.

7. Future Prospects

Nanotechnology, biotechnology, and information technology are moving closer together, following an accelerated path of unparalleled breakthroughs. Their focus on human dimensions is still emerging but promises to dominate the next decades. Despite efforts of workshop organizers, given the breadth of the topic, it was impossible to recruit leading experts in all the areas where the convergence of NBIC technologies is likely to have a significant impact in 10 to 20 years. In addition, work has really not begun in some of the key application areas, and new areas are likely to emerge that have not yet attracted the attention of many scientists and engineers. Thus, the section below presents the following *admittedly speculative*

additional ideas on how technological convergence may transform human abilities two decades and more in the future. Many of the ideas that follow emerged during the workshop, and others were suggested in discussions with participants afterward.

Work Efficiency

Improvement of human physical and mental performance, at both the individual and group level, can increase productivity greatly. Several concepts are in development that could enhance working environments (cf. IBM 2002). To remain competitive, American industry must continue to find ways to improve quality and efficiency (Mowery 1999; Jorgenson and Wessner 2002). Nanotechnology promises to become an efficient length scale for manufacturing (NSTC 2002) because rearranging matter at the nanoscale via weak molecular interactions would require less energy and material. The recent trend toward intensive electronic monitoring and just-in-time inventories has reduced waste, but tightening the

Table 2. Key visionary ideas and projects discussed in this report

Theme	Key visionary ideas/projects
A. Overall Potential of Converging Technologies	NBIC strategy for technological and economical competitiveness
	New patterns for S&T, economy, and society
	Enhancing individual and group abilities, productivity, and learning
	Sustainable and "intelligent" environments
	Changing human activities towards the "innovation age"
B. Expanding Human Cognition and Communication	Human cognome project and cognitive evolution
	Brain-to-brain interactions and group communication
	Spatial cognition and visual language using converging technologies
	Enhanced tools for learning and creativity
	Predictive science of societal behavior
C. Improving Human Health and Physical Capabilities	Healthcare, body replacements, and physiological self-regulation
	Brain-machine interfaces and neuromorphing engineering
	Improving sensorial capacities and expanding functions
	Improving quality of life of disabled people
	Aging with dignity and life extension
D. Enhancing Group and Societal Outcomes	The Communicator: enhancing group interaction and creativity
	Cognitive engineering and enhancing productivity
	Revolutionary products, including "aircraft of the future"
	Networked society, with bio-inspired culture
E. National Security	Enhancing physical and mental capacity of a soldier
	Enhancing readiness and threat anticipation tools
	Globally linked detection devices
	Uninhabited combat vehicles
F. Unifying Science and Education	Unifying science from the nanoscale and integrative principles
	Cognitive, civic, and ethical changes in a networked society
	Breadth, depth, "trading zones," and reshaping education at all levels
	Changing the human culture

efficiency of manufacturing and distribution supply chains could prove to be a one-time-only improvement in profitability that could not be duplicated in the future (National Research Council 2000).

However, application of new generations of convergent technology has the potential to provide better value to customers at lower cost to producers, offering the possibility of further profitability improvements. For example, even more intensive use of information technology in conjunction with nanotechnology, biotechnology, and cognitive sciences could reduce waste and pollution costs and permit very rapid reconfiguration of manufacturing processes and product lines (National Research Council 1998). Business and industry are already beginning to restructure themselves on a global scale as network-based organizations following fundamentally new management principles.

Biology in conjunction with nanoscale design and IT control has the potential to contribute both abstract models and specific physical processes to the development of customer-centric production that blends the principles of custom-design craftsmanship (which maximizes customer satisfaction) with the principles of assembly-line mass production (which minimizes production costs). In the gestation of higher animals, a single fertilized egg cell differentiates rapidly into specialized cells that grow into very different organs of the body, controlled in a complex manner by the messenger chemicals produced by the cells themselves. Whether based in nanotechnology, information technology, biotechnology, or cognitive-based technology, new adaptive production systems could be developed that automatically adjust design features in a way analogous to the growing embryo, without the need to halt production or retool. Convergence of these four technologies could also develop many bio-inspired processes for "growing" key components of industrial products, rather than wastefully machining them out of larger materials or laboriously assembling them from smaller parts (cf. National Research Council 1999).

The Human Body and Mind Throughout the Life Cycle

Improving perceptual capabilities, biohybrid systems, exoskeletons, and metabolic enhancement can be considered for human performance augmentation. Medical implants for sensory replacement, including multiple sensory modalities for visually and hearing-impaired persons, and direct brain-machine interfaces are real possibilities. Controlled metabolism in cells, specific tissues, organs, or the entire body is possible. One application would be increased endurance and resistance to sleep deprivation; another is a method of optimizing oxygenization of blood when metabolism is compromised in a critical medical situation. Others would be realtime genetic testing so that individually tailored drugs can be provided to patients, and an artificial pancreas that would monitor and adjust the release of hormones in the human body.

Increasing intellectual capabilities requires understanding the brain and simulating its processes. Knowledge about the structure, function, and occasional dysfunction of the human mind will provide new ways to increase cognitive capabilities (Steve et al. 2002; National Research Council 1988). Reverse engineering of the human brain may be accomplished in the next two decades that would allow for better understanding of its functions. An artificial brain (Cauller and Penz 2002) could be a tool for discovery, especially if computers could closely

simulate the actual brain. It would be revolutionary to see if aspects of human consciousness could be transferred to machines (Kurzweil 1999) in order to better interact with and serve humans.

Sustaining human physical and mental abilities throughout the life span would be facilitated by progress in neuroscience (Stern and Carstensen 2000) and cellular biology at the nanoscale. An active and dignified life could be possible far into a person's second century, due to the convergence of technologies (cf. Saxl 2002). Gene therapy to cure early aging syndromes may become common, giving vastly improved longevity and quality of life to millions of people (Bonadio 2002; Heller 2002; Connolly 2002).

Communication and Education

New communication paradigms (brain-to-brain, brain-machine-brain, group) could be realized in 10 to 20 years. Neuromorphic engineering may allow the transmission of thoughts and biosensor output from the human body to devices for signal processing. Wearable computers with power similar to that of the human brain will act as personal assistants or brokers, providing valuable information of every kind in forms optimized for the specific user. Visual communication could complement verbal communication, sometimes replacing spoken language when speed is a priority or enhancing speech when needed to exploit maximum mental capabilities (Horn 2002; Hewlett Packard 2002).

People will be able to acquire a radically different instinctive understanding of the world as a hierarchy of complex systems rooted in the nanoscale. Advances in cognitive science will enable nanoscience education, by identifying the best ways for students to conceptualize nanostructures and processes at increasingly advanced stages in their learning (National Institute of Mental Health 2002). Education at all levels will exploit augmented reality, in which multimedia information displays are seamlessly integrated into the physical world. Strategies for hierarchical, architectural, and global analysis and design of complex systems will help integrate the curriculum of schools and inform management decisions across a diverse range of fields.

Mental Health

In many respects, perhaps the most difficult challenge we face in improving human performance is understanding and remediating mental illness (Anderson 1997). For fully the past two centuries, psychiatry has alternated between periods of optimism and pessimism, as well as between competing psychological, social, physiological, chemical, and genetic theories of mental illness. We can hope that these disputes will be resolved through physiological and psychological understanding of mental processes, and that scientific convergence will achieve lasting cures through a combination of biological and cognitive treatments, all assisted by information and nanoscale technologies.

Nanotechnology will provide means to deliver medications to the exact location within the brain where they are needed, thus minimizing negative side effects elsewhere in the nervous system. The convergence of cognitive science with nano-, bio-, and information technologies should permit systematic evaluation of the bewildering range of current psychiatric theories and therapies, and allow clinicians to improve the best treatments. It is also possible that convergent communications

and robotics technologies may produce an entirely new category of prosthetic or assistive devices that can compensate for cognitive or emotional deficiencies.

Aeronautics and Space Flight

NBIC synergies could greatly expand capabilities for piloted adaptive aircraft, unmanned aircraft, and human space flight. Nanostructured materials and advanced electronics have the promise of reducing the weight of spacecraft by three quarters in the next 10 to 20 years. Specific subsystems for human space flight may also be revolutionized by the same combination of technologies, for example durable but light and self-repairing spacesuits, high-performance electronics with low demands for electric power, and low-cost but high-value large orbiting structures. If the problems of orbital launch costs and efficient subsystems can be solved, then human society can effectively exploit Earth orbital space, the Moon, asteroids, and the planet Mars. Several participants in the workshop noted the potential for intelligent machines of the future to take on progressively more human characteristics, so we can well imagine that the first pioneers that take "humanity" far into space will be descendents of Pathfinder and the Voyagers that will be endowed with intelligence and communication capabilities reflecting human behavior.

Food and Farming

Farmers have long appreciated the advantages of science and technology; the convergence of nanotechnology, biotechnology, and information technology could significantly improve their effectiveness. For example, nanoscale genetics may help preserve and control food production. Inexpensive nano-enabled biosensors could monitor the health and nutrition of cattle, transmitting the data into the farmer's personal computer that advises him about the care the animals need. In the same way, sensors distributed across farmland could advise the farmer about the need for water and fertilizer, thus avoiding wastage and achieving the most profitable acreage crop yield (National Research Council 1997). Bio-nano convergence can provide new ways of actually applying the treatment to the crops, increasing the efficiency of fertilizers and pesticides.

Use of nano-enabled biosensors would monitor freshness to help grocers avoid selling stale goods and to avoid the wastage of discarding perfectly good packaged food that has merely reached an arbitrary shelf life date. The consumer should have access to the same information, both before and after purchase. Many consumers are dissatisfied with the limited information about ingredients on many packaged foods, and the total lack of information about foods served in restaurants. Convergent technologies could provide portable instruments, for example packaged into a pen-like device or perhaps a ring, that could instantly tell the consumer how much sodium, fats, or allergenic substances a food contains.

Sustainable and Intelligent Environments

Sustainable resources of food, water, energy, and materials are achievable through converging technologies. Exact manufacturing, exact integration in biosystems, and IT control will help stabilize the supply of resources. Value will stem from information, including that embodied in the complex structure of manufactured items made from the nanoscale out of common chemical elements, rather than rare metals or nonrenewable energy supplies. Sensing the environment and biosystems of the world will become essential in global environmental

monitoring and remediation. New sources for a distributed energy system are envisioned, as well as new solutions such as highly efficient photosynthetic proteins, membranes, and devices.

Interactive and "intelligent" environments for human activities are envisioned, responding to advancements in areas such as neuro-ergonomics and the needs of persons with disabilities.

External surfaces of buildings could automatically change shape and color to adjust to different conditions of temperature, lighting, wind, and precipitation. Once the science, manufacturing processes, and economic markets have developed sufficiently, adaptive materials need not be especially expensive, especially when their increased performance and energy efficiency are factored in. For example, nanotechnology materials and IT-assisted design could produce new, durable house paints that change color, reflecting heat on hot days and absorbing heat on cold days. Indoors, ordinary walls could be vast computer displays, capable of enhancing the residents' aesthetic experience by displaying changing virtual artworks and wallpapers. Adaptive materials could obtain their energy from temperature differentials between different surfaces (thermocouples) or naturally occurring vibrations (piezoelectric), rather than requiring electrical input. The ability to engineer inexpensive materials on the nanoscale will be crucial, and information technology can help design the materials as well as be designed into some of the adaptive systems. There also will be a role for cognitive science, because architects need to take account of human needs and the often unexpected ways that human beings respond to particular design features.

Self-Presentation and Fashion

Government-supported academic researchers frequently ignore many economically important industries, in part because those industries traditionally have not involved advanced technology but also perhaps because they were not perceived as "serious" fields. Among these are clothing fashions, jewelry, and cosmetics. Stereotypes aside, these are multibillion dollar industries that could benefit from the new opportunities afforded by convergent technologies. In social life, physical attractiveness is very important. Anything that enhances a person's beauty or dignity improves that individual's performance in relations with other people.

Convergence of nanotechnology and biotechnology with cognitive science could produce new kinds of cosmetics that change with the user's moods, enhancing the person's emotional expressiveness. Components of wearable computers could be packaged in scintillating jewelry, automatically communicating thoughts and feelings between people who are metaphorically and electronically "on the same wave length." Biotechnology could produce new materials that would be combined in manufacturing with nanotechnology-based information technology to produce clothing that automatically adjusts to changing temperatures and weather conditions. Perhaps the colors and apparent textures of this "smart clothing" would adjust also to the wearer's activities and social environment.

Transformation of Civilization

The profound changes of the next two decades may be nothing compared to the utter transformation that may take place in the remainder of the 21st century. Processes both of decentralization and integration would render society ever more

complex, resulting in a new, dynamic social architecture. There would be entirely new patterns in manufacturing, the economy, education, and military conflict.

People may possess entirely new capabilities for relations with each other, with machines, and with the institutions of civilization. In some areas of human life, old customs and ethics will persist, but it is difficult to predict which realms of action and experience these will be. Perhaps wholly new ethical principles will govern in areas of radical technological advance, such as the acceptance of brain implants, the role of robots in human society, and the ambiguity of death in an era of increasing experimentation with cloning. Human identity and dignity must be preserved. In the same way in which machines were built to surpass human physical powers in the industrial revolution, computers can surpass human memory and computational speed for intended actions. The ultimate control will remain with humans and human society. With proper attention to safeguards, ethical issues, and societal needs, quality of life could increase significantly.

New professions for humans and new roles for machines may arise to mediate between all this complexity and the individual person. Art, music, and literature may reach new levels of subtlety and sophistication, enhancing the mental qualities of life and the innate human appreciation for beauty.

A networked society of billions of human beings could be as complex compared to an individual human being as a human being is to a single nerve cell. From local groups of linked enhanced individuals to a global collective intelligence, key new capabilities would arise from relationships created with NBIC technologies. Such a system would have distributed information and control and new patterns of manufacturing, economic activity, and education. It could be structured to enhance individuals' creativity and independence. Far from unnatural, such a collective social system may be compared to a larger form of a biological organism. Biological organisms themselves make use of many structures such as bones and circulatory system. The networked society enabled through NBIC convergence could explore new pathways in societal structures, in an increasingly complex system (Bar-Yam 1997).

It may be possible to develop a predictive science of society and to apply advanced corrective actions, based on the convergence ideas of NBIC. Human culture and human physiology may undergo rapid evolution, intertwining like the twin strands of DNA, hopefully guided by analytic science as well as traditional wisdom. As Table 3 suggests, the pace of change is accelerating, and scientific convergence may be a watershed in history to rank with the invention of agriculture and the Industrial Revolution.

8. Recommendations

The recommendations of this report are far-reaching and fundamental, urging the transformation of science at its very roots. But the recommendations also seek to preserve the wonderful accomplishments of science and sustain the momentum of discovery that has been energized by generations of scientists. Only by evolving can science continue to thrive and make the vast contributions to society that it is capable of in the coming decades. There are outstanding opportunities that were not

available in the past. The new developments will be revolutionary and must be governed by respect for human welfare and dignity.

Specific Areas for Research and Education Investment

The research and education needs are both deep and broad. In order to connect disciplines at their interfaces, understand and assemble matter from its building blocks, while focusing on a broad systems perspective and improving human performance, research and education must have deep scientific roots and superior communication among the fields of human endeavor.

Table 3. History of some very significant augmentations to human performance: Improving our ability to collectively improve ourselves (see also Spohrer 2002)

Generations	Several Key Advancements (human kind, tools and technology, communication)
-m	Cell, body and brain development
- 100,000	Old Stone Age (Paleolithic), Homo Erectus, speech
-10,000	Homo Sapiens, making tools
-500	Mesolithic, creating art
-400	Neolithic, agricultural products, writing, libraries
-40	Universities
-24	Printing
-16	Renaissance in S&T, accurate clocks
-10	Industrial revolution
-5	Telephone
-4	Radio
-3	TV
-2	Computers
-1	Microbiology, Internet
0	Reaching at the building blocks of matter (nanoscience) Biotechnology products Global connection via Internet; GPS/sensors for navigation
½	Unifying science and converging technologies from the nanoscale Nanotechnology products Improving human performance advancements Global education and information infrastructure
1	Converging technology products for improving human physical and mental performance (new products and services, brain connectivity, sensory abilities, etc.) Societal and business reorganization
n	Evolution transcending human cell, body, and brain?

The following general integrative approaches have been identified as essential to NBIC:

- Development of NBIC tools for investigation and transformational engineering at four levels: nano/microscopic, individual, group, and society
- Integration of fundamental concepts of NBIC across all scales, beginning with the nanoscale
- Investigation of converging technologies that is systems- and holistic-based

- Focus of future technological developments on implications for improving human performance

These principles concern the research methods, theoretical analyses, systemic perspective, and human benefit dimensions of scientific and technological integration. Sharing research techniques and engineering tools is one way that scientists in traditionally different fields can integrate their work. Another is utilization of similar ideas, mathematical models, and explanatory language. Expected to be a major challenge in approaching complex systems is the hierarchical architecture in which various components are integrated and used. Consideration of the human implications of converging technologies will include examination of potential unexpected consequences of NBIC developments, including ethical and legal aspects.

Recommendations to Individuals and Organizations

This report has educational and transformational goals. Building on the suggestions developed in the five topical groups and on the ideas in the more than 50 individual contributions, workshop participants recommended a **national R&D priority area on converging technologies focused on enhancing human performance.** The main transforming measures are outlined in section 4 of this summary. The opportunity now is broad, enduring, and of general interest. The report contributors addressed the roles that individuals, academe, the private sector, the U.S. Government, professional societies, and other organizations should play in this converging technology priority area:

a) **Individuals.** Scientists and engineers at every career level should gain skills in at least one NBIC area and in neighboring disciplines, collaborate with colleagues in other fields, and take risks in launching innovative projects that could advance technology convergence for enhancing human performance.

b) **Academe.** Educational institutions at all levels should undertake major curricular and organizational reforms to restructure the teaching of science and engineering so that previously separate disciplines can converge around common principles to train the technical labor force for the future. The basic concepts of nanoscience, biology, information, and cognitive sciences should be introduced at the beginning of undergraduate education; technical and humanistic degrees should have common courses and activities related to NBIC and the human dimensions of science and technology. Investigations of converging technologies should focus on the holistic aspects and synergism. The hierarchical architecture in which various components are integrated and used is expected to be a major challenge.

c) **Private Sector.** Manufacturing, biotechnology, and information service corporations will need to develop partnerships of unparalleled scope to exploit the tremendous opportunities from technological convergence, engaging in joint ventures with each other, establishing research linkages with universities, and investing in production facilities based on entirely new principles and materials, devices, and systems.

d) **Government.** A national research and development priority area should be established to focus on converging technologies that enhance human performance. Organizations should provide leadership to coordinate the work

of other institutions and must accelerate convergence by supporting new multidisciplinary scientific efforts while sustaining the traditional disciplines that are essential for success. Special effort will be required to identify future technological developments; explore their implications for human performance; study unexpected consequences of NBIC developments; and consider ethical, legal, and policy issues. Governments must provide support for education and training of future NBIC workers and to prepare society for the major systemic changes envisioned for a generation from now. Policymakers must envision development scenarios to creatively stimulate the convergence. Ethical, legal, moral, economic, environmental, workforce development, and other societal implications must be addressed from the beginning, involving leading NBIC scientists and engineers, social scientists and a broad coalition of professional and civic organizations. Research on societal implications must be funded, and the risk of potential undesirable secondary effect must be monitored by a government organization in order to anticipate and take corrective actions. Tools should be developed to anticipate scenarios for future technology development and applications. The transforming measures outlined in section 4 above suggest the dimensions of the Federal Government role.

e) **Professional Societies.** The scientific community should create new means of interdisciplinary training and communication, reduce the barriers that inhibit individuals from working across disciplines, aggressively highlight opportunities for convergence in their conferences, develop links to a variety of other technical organizations, and address ethical issues related to technological developments. Through mechanisms like conferences and publications, professional societies can seed NBIC ideas in learning organizations, funding agencies, and the society at large.

f) **Other Organizations.** Nongovernmental organizations that represent potential user groups should contribute to the design and testing of convergent technologies and recommend NBIC priorities, in order to maximize the benefits for their diverse constituencies. Private research foundations should invest in NBIC research in those areas that are consistent with their particular missions. The public media should increase high-quality coverage of science and technology, on the basis of the new convergent paradigm, to inform citizens so they can participate wisely in debates about ethical issues such as the unexpected effects on social equality, policies concerning diversity, and the implications of transforming human nature.

A vast opportunity is created by the convergence of sciences and technologies starting with integration from the nanoscale, having immense individual, societal, and historical implications for human development. Therefore, the contributors to this report recommend *a national research and development priority area on converging technologies focused on enhancing human performance*. Advancing knowledge and transforming tools will move our activities from simple repetitions to creative, innovative acts and transfer the focus from machines to human development. Converging technologies are at the confluence of key disciplines and areas of application, and the role of government is important because no other

participant can cover the breadth and level of required collective effort. Without special efforts for coordination and integration, the path of science might not lead to the fundamental unification envisioned here. Technology will increasingly dominate the world, as population, resource exploitation, and potential social conflict grow. Therefore, the success of this convergent technologies priority area is essential to the future of humanity.

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GENERAL STATEMENTS AND VISIONARY PROJECTS

The following six sets of contributions (chapters A to F) present key statements and visions from academe, private sector and government illustrating what technological convergence could achieve in the next 10 to 20 years. In each set, statements are grouped at the beginning that consider the current situation in the particular area and project ways we could build on it to achieve rapid progress. The later contributions in the set present visions of what might be achieved toward the end of the two-decade period. In the first of these six sets, government leaders and representatives of the private sector provide the motivation for this effort to understand the promise of converging technologies. The second and third sets of contributions identify significant ways in which the mental and physical abilities of individual humans could be improved. The third and fourth sets examine prospects on the group and societal level, one considering ways in which the internal performance of the society could benefit and the other focusing on the defense of the society against external threats to its security. The sixth and final set of essays considers the transformation of science and engineering themselves, largely through advances in education.

A. MOTIVATION AND OUTLOOK

THEME A SUMMARY

Panel: P. Bond, J. Canton, M. Dastoor, N. Gingrich, M. Hirschbein, C.H. Huettner, P. Kuekes, J. Watson, M.C. Roco, S. Venneri, R.S. Williams

In a sense, this section of the report gives the authors their assignment, which is to identify the technological benefits of convergence that could be of greatest value to human performance and to consider how to achieve them. Five of the statements were contributed by representatives of government agencies: The Office of Science and Technology Policy, The Department of Commerce, The National Aeronautics and Space Administration, the National Institutes of Health, and the National Science Foundation. The remaining three were contributed from private sector organizations: The American Enterprise Institute, Hewlett Packard, and the Institute for Global Futures. But these eight papers are far more than mission statements because they also provide an essential outlook on the current technological situation and the tremendous potential of convergence.

1. It is essential to identify new technologies that have great potential to improve human performance, especially those that are unlikely to be developed as a natural consequence of the day-to-day activities of single governmental, industrial, or educational institutions. Revolutionary technological change tends to occur outside conventional organizations, whether through social movements that promulgate new goals, through conceptual innovations that overturn old paradigms of how a goal can be

achieved, or through cross-fertilization of methods and visions across the boundaries between established fields (Bainbridge 1976). Formal mechanisms to promote major breakthroughs can be extremely effective, notably the development of partnerships between government agencies to energize communication and on occasion to launch multiagency scientific initiatives.

2. Government has an important role in setting long-term priorities and in making sure a national environment exists in which beneficial innovations will be developed. There must be a free and rational debate about the ethical and social aspects of potential uses of technology, and government must provide an arena for these debates that is most conducive to results that benefit humans. At the same time, government must ensure economic conditions that facilitate the rapid invention and deployment of beneficial technologies, thereby encouraging entrepreneurs and venture capitalists to promote innovation. Of course, government cannot accomplish all this alone. In particular, scientists and engineers must learn how to communicate vividly but correctly the scientific facts and engineering options that must be understood by policymakers and the general public, if the right decisions are to be made.
3. While American science and technology benefit the entire world, it is vital to recognize that technological superiority is the fundamental basis of the economic prosperity and national security of the United States. We are in an Age of Transitions, when we must move forward if we are not to fall behind, and we must be ready to chart a course forward through constantly shifting seas and winds. Organizations of all kinds, including government itself, must become agile, reinventing themselves frequently while having the wisdom to know which values are fundamental and must be preserved. The division of labor among institutions and sciences will change, often in unexpected ways. For many years, scholars, social scientists, and consultants have been developing knowledge about how to manage change (Boulding 1964; Drucker 1969; Deming 1982; Womack and Jones 1996), but vigorous, fundamental research will be needed throughout the coming decades on the interaction between organizations, technology, and human benefit.
4. Government agencies need progress in NBIC in order to accomplish their designated missions. For example, both spacecraft and military aircraft must combine high performance with low weight, so both NASA and the Department of Defense require advances in materials from nanotechnology and in computing from information technology. Furthermore, in medicine and healthcare, for example, national need will require that scientists and engineers tackle relatively pedestrian problems, whose solutions will benefit people but not push forward the frontiers of science. But practical challenges often drive the discovery of new knowledge and the imagination of new ideas. At the same time, government agencies can gain enhanced missions from NBIC breakthroughs. One very attractive possibility would be a multiagency initiative to improve human performance.
5. Science must offer society new visions of what it is possible to achieve. The society depends upon scientists for authoritative knowledge and professional judgment to maintain and gradually improve the well-being of citizens, but

scientists must also become visionaries who can imagine possibilities beyond anything currently experienced in the world. In science, the intrinsic human need for intellectual advancement finds its most powerful expression. At times, scientists should take great intellectual risks, exploring unusual and even unreasonable ideas, because the scientific method for testing theories empirically can ultimately distinguish the good ideas from the bad. Across all of the sciences, individual scientists and teams should be supported in their quest for knowledge. Then interdisciplinary efforts can harvest discoveries across the boundaries of many fields, and engineers will harness them to accomplish technological progress.

The following eight statements develop these and other ideas more fully, thereby providing the motivation for the many chapters that follow. They also provide a perspective on the future by identifying a number of megatrends that appear to be dominant at this point in human history and by suggesting ways that scientists and policymakers should respond to these trends. Their advice will help Americans make history, rather than being subjects of it, strengthening our ability to shape our future. The statements include a message from the White House Office of Science and Technology Policy (OSTP) concerning the importance of this activity to the nation, a message from the Department of Commerce on its potential impact on the economy and U.S. competitiveness, a vision for converging technologies in the future, examples of activities already underway at NASA and NIH, industry and business perspectives on the need for a visionary effort, and an overview of the trend toward convergence of the megatrends in science and engineering.

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NATIONAL STRATEGY TOWARDS CONVERGING SCIENCE AND TECHNOLOGY

Charles H. Huettner, OSTP, White House

Good morning. I want to express to you on behalf of Dr. John Marburger, who is the President's science advisor and the Director of the Office of Science and Technology Policy (OSTP), his regrets for not being able to be with you,

particularly because this workshop is a very important first step towards the future in which different sciences come together.

The role of the OSTP is to identify cross-cutting, high-risk technologies that don't reside in a particular department or agency and to sponsor them, thus helping them move across government agencies. Nanotechnology is a clear example of the kinds of technologies that have great potential and yet need government-wide review and focus.

Obviously, nanotechnology is just one of a number of emerging technologies. We are living in a very exciting time. Just think of what has happened with information technology over the last 10 years. It has allowed us to have the Internet, a global economy, and all of the things that we know about and have been living through. In just this past year, the field of biology has experienced tremendous advances with the human genome project. New this year in the budget is the national nanotechnology initiative, and similar kinds of progress and accomplishment are anticipated there.

Could these technologies and others merge to become something more important than any one individually? The answer to that question obviously is that they must. Convergence means more than simply coordination of projects and groups talking to one another along the way. It is imperative to integrate what is happening, rise above it, and get a bigger picture than what is apparent in each individual section.

There is an institute at Harvard called the Junior Fellows, formed many, many years ago by a forward thinker at Harvard and endowed with a beautiful building with a wonderful wine cellar. Senior Fellows, who were the Nobel Laureates of the university, and Junior Fellows, who were a select group of people picked from different disciplines, came together there for dinner from time to time. Sitting together at one Junior Fellows dinner I attended several years ago were musicians, astrophysicists, and astronomers discussing how certain musical chords sound good and others don't, and how those sorts of harmonics actually could help to explain the solar system, the evolution of galaxies, and so forth. Essentially, this is what the two-day NBIC workshop is doing, bringing together thinkers from different disciplines to find common ground and stimulate new thinking. When professionals as diverse as musicians and astrophysicists can discover mutually resonant concepts, think about what we can do with the kinds of technologies that we have today. That is why this NBIC workshop is so important.

You are the national technology leaders, or you are connected with them. You are the beginnings of an important group coming together. Nuclear and aerospace technology, psychology, computer science, chemistry, venture capital, medicine, bioengineering, social sciences — you're all here, and you represent not only the government, but also industry and academia. I thought it was tremendously creative, the way that the working sessions were broken down around people's needs because, in the end, that's why science is here. Science is here to serve people. So, it is very important for the breakout groups to look at human cognition and communications and human physical performance by focusing on how to solve human needs.

Take this opportunity to begin the cross-fertilization and understanding of each other's disciplines. The language of each technology is different. The key ideas that define them are different. The hopes and visions are different. The needs to

accomplish those are different. But the network that we can form and the learning that we can have as a result of today's efforts can somehow bridge those gaps and begin the understanding.

I applaud you for being here today. I challenge you to learn and think beyond your discipline to help to establish the inner technology visions, connections, and mechanisms that will solve the human problems of our world. This is the beginning of the future, and we at OSTP are both anxious to help and anxious to learn from you.

CONVERGING TECHNOLOGIES AND COMPETITIVENESS

The Honorable Phillip J. Bond, Undersecretary for Technology, Department of Commerce

Good morning, and thank you all. It is a pleasure to be here as a co-host, and I want to give you all greetings on behalf of Secretary of Commerce Don Evans, whom I am thrilled and privileged to serve with in the Bush administration. Thank you, Mike Roco and Joe Bordogna for bringing us all together. Charlie Huettner, please give my best wishes to Jack Marburger. Dr. Marburger and I were confirmation cousins, going through our Senate hearings and then floor consideration together.

It is a rare thing to see people inside the Washington Beltway coming together to actually think long-term in a town that is usually driven by the daily headlines. I believe it was George Will who observed that most people inside the Beltway survive on the intellectual capital they accumulated before they came inside the Beltway. I certainly hope that's not true in my case. I do want to encourage you and join you. Let us lift our eyes, look at the future, and really seize the opportunity for some of the policy implications.

I stand before you today not as a scientist, but as an advocate. My background as the head of Hewlett-Packard's office here in Washington, before that with an IT association, and then on the Hill, and before that with Dick Cheney at the Pentagon, implies that I am supposed to know something about moving the gears of government toward positive policy outcomes. With that in mind, I now have the privilege of overseeing the National Institute of Standards and Technology (NIST), the Office of Technology Policy, and the National Technical Information Service that I am sure many of you periodically go to for information, as well as the National Medal of Technology.

I am sure that many of you saw the news this morning that one of our past National Medal of Technology winners has unveiled what was previously code-named Ginger, which I now understand is the Segway Human Transporter — Dean Kamen's new project. So, next time we can all ride our two-wheelers to the meeting. At any rate, I want to pledge to you to really try to provide the kind of support needed over the long term on the policy front.

Historical perspective is useful for a meeting such as this, and for me this is best gained in very personal terms. My grandparents, Ralph and Helen Baird, just passed away. He died earlier this year at 101 and she two years ago at 99. They taught me about the importance of science and technology to the human condition. Before they

passed on, they sat down and made a videotape reviewing the things they had seen in their life.

In that arena, what was particularly relevant is the fact that Ralph had been a science teacher. Both of my grandparents saw men learn to fly and to mass-produce horseless carriages. They told great stories about living in Kansas and getting on the community phone, ringing their neighbors and saying, "Quick, run down to the road. One's coming. Run down to see one of these gizmos rolling by." They saw the generation and massive transmission of electricity, the harnessing of the power of the atom, the space-travel to our moon, the looking back in time to the origins of our universe, the development of instantaneous global communications, and most recently, the deciphering of the human genome and cloning of very complex organisms. Each of these is extraordinary in its technical complexity but also profound in terms of its economic and social significance.

This is one of the challenges we have for you in the discussions. To borrow from Churchill, as everybody seems to do, this is "the end of the beginning." As we head into the 21st Century, we are going to have not only accelerating change, but accelerating moral and ethical challenges. Again here, I take a very personal view of this. My daughters Jackie and Jesse are 10 and 7. So when I look at the future and think about the ethical possibilities and possibilities of robo-sapiens, as *Wired* magazine talks about, I think in terms of what my daughters will face and how we as a society can reap the harvest of technology and remove the chaff of unethical uses of that technology. We have a real balancing act moving forward. The future of all of us — and my daughters' futures — are on the line.

Other speakers have mentioned the exciting fields that you're going to be looking at today and how they converge. I will leave most of the description of that to others, including the always provocative and mesmerizing Newt Gingrich and my friend Stan Williams from HP, and to your breakout discussions. However, as a political appointee, let me do what I do best, and that is to observe the obvious.

Obviously, powerful technologies are developing. Each is powerful individually, but the real power is synergy and integration, all done at the nanoscale. There's plenty of room at the bottom. Intel recently announced it expects to produce a terahertz chip about six or seven years out — 25 times the number of transistors as the top-of-the-line Pentium 4. Within the next few years we're going to be looking at computers that are really personal brokers or information assistants. These devices will be so small that we'll wear them and integrate them. They will serve as information brokers. Again, when I think about my daughters, if current trends hold, one of those information brokers will be looking at science and horses and the other will be looking at hairstyles — but to each their own. Seriously, that day is coming fast, based on breakthroughs in producing computer chips with extremely small components. If we do policy right, with each breakthrough will come technology transfer, commercialization, economic growth, and opportunity that will pay for the next round of research.

In all of this, at least as a policy person, I try to separate hype from hope. But the more I thought about that, the more I determined that in this political town, maybe the separation isn't all that important, because hype and hope end up fueling the social passion that forms our politics. It gets budgets passed. It makes things possible for all of you. Without some passion in the public square, we will not

achieve many of our goals. Those goals are mind-boggling — what we used to think of as miraculous — the deaf to hear, the blind to see, every child to be fed. And that's just for starters.

Always, each advance in technology carries a two-edged sword. As a policy person I need your help. One hundred years ago, the automobile was not immediately embraced; it was rejected as a controversial new innovation. Eventually it was accepted, then we had a love affair with it, and now it's perhaps a platonic relationship. Our journey with these other technologies is going to have similar bumps in the road. And so, as you set out today, I think you should include these three important considerations in your mission:

- to achieve the human potential of everybody
- to avoid offending the human condition
- to develop a strategy that will accelerate benefits

Earlier, we talked about the network effect of bringing you all together, and these new technologies are going to enhance group performance in dramatic ways, too. We really must look at some of the ethical challenges that are right around the corner or even upon us today. Our strategy must establish priorities that foster scientific and technical collaboration, and ensure that our nation develops the necessary disciplines and workforce. We need a balanced but dynamic approach that protects intellectual property, provides for open markets, allows commercialization, and recognizes that American leadership is very much at stake.

Look all around the globe at the work that's going on at the nanoscale. American leadership is at stake, but we need a global framework for moving forward. The federal government, of course, has an important role: ensuring a business environment that enables these technologies to flourish, to work on that global aspect through the institutions of government, to continue to provide federal support for R&D. I am proud that President Bush recommended a record investment in R&D. I know there are concerns about the balance of the research portfolio. We need your help on that. President Bush specifically requested a record increase in the nano budget, over $604 million, almost double what it was two years ago.

The federal government has a clear fiscal role to play but also should use the bully pulpit to inspire young kids like one daughter of mine who does love science right now, so that they will go ahead and pursue careers like yours to reach the breakthroughs, so we will have more people like 39-year-old Eric Cornell at NIST, one of our recent winners of a Nobel Prize for Physics.

I think we can achieve our highest aspirations by working together as we are today — and we've got some of the best minds gathered around this table. But my message is distilled to this: If we set the right policies and we find the right balance, we can reap the rewards and avoid the really atrocious unethical possibilities. At every step — whether it's funding, advocacy, policy formation, public education, or commercialization — we're going to need you scientists and engineers to be intimately involved. I look forward to being a part of this promising effort. Thank you.

VISION FOR THE CONVERGING TECHNOLOGIES

Newt Gingrich

My theme is to argue that you want to be unreasonable in your planning.

I was struck with this at the session Mike Roco invited me to about six months ago, where somebody made a very impassioned plea against promising too much too quickly and not exaggerating. In 1945, Vannevar Bush wrote what was a quite unreasonable article for his day, about the future of computational power. Einstein's letter to Franklin Delano Roosevelt in September of 1939 was an extremely unreasonable letter. Edward Teller told me recently that he got in a big argument with Niels Bohr about whether or not it was possible to create an atomic bomb. Bohr asserted emphatically, it would take all of the electrical production capacity of an entire country. Teller said they didn't meet again until 1944 when they were at Los Alamos and Bohr yelled down the corridor "You see, I was right." By Danish standards, the Manhattan Project was using all the power of an entire country.

Vannevar Bush's classic article is a profound, general statement of what ultimately became the ARPANET, Internet, and today's personal computation system. At the time it was written, it was clearly not doable. And so, I want to start with the notion that at the visionary level, those who understand the potential have a real obligation to reach beyond any innate modesty or conservatism and to paint fairly boldly the plausible achievement.

Now, in this case you're talking about converging technology for improving human performance. Perhaps you should actually put up on a wall somewhere all of the achievable things in each zone, in the next 20 years, each of the stovepipes if you will. And then back up and see how you can move these against each other. What does the combination make true?

Think about the nanoscale in terms of a whole range of implications for doing all sorts of things, because if you can in fact get self-assembly and intelligent organization at that level, you really change all sorts of capabilities in ways that do in fact boggle the imagination, because they are that remarkable. If you bring that together with the biological revolution, the next 20 years of computation, and what we should be learning about human cognition, the capability can be quite stunning. For example, there's no reason to believe we can't ultimately design a new American way of learning and a new American way of thinking about things.

You see some of that in athletics, comparing all the various things we now do for athletes compared to 40 years ago. There is a remarkable difference, from nutrition to training to understanding of how to optimize the human body, that just wasn't physically possible 40 years ago. We didn't have the knowledge or the experience. I would encourage you first of all to put up the possibilities, multiply them against each other, and then describe what that would mean for humans, because it really is quite astounding.

I was an army brat in an era when we lived in France. In order to call back to the United States you went to a local post office to call the Paris operator to ask how many hours it would be before there would be an opening on the Atlantic cable. When my daughter was an *au pair*, I picked up my phone at home to call her cell phone in a place just south of Paris. Imagine a person who, having gotten cash out of an ATM, drives to a self-serve gas station, pays with a credit card, drives to work on

the expressway listening to a CD while talking on a digital cell phone, and then says, "Well, what does science do for me?"

This brings me to my second point about being unreasonable. *When you lay out the potential positive improvements for the nation, for the individual, for the society, you then have to communicate that in relatively vivid language.*

People like Isaac Asimov, Arthur C. Clarke, and Carl Sagan did an amazing amount to convince humans that science and technology were important. Vannevar Bush understood it at the beginning of the Second World War. But if those who know refuse to explain in understandable language, then they should quit griping about the ignorance of those who don't know. Science can't have it both ways. You can't say, "This is the most important secular venture of mankind; it takes an enormous amount of energy to master it, and by the way, I won't tell you about it in a language you can understand." Scientists have an obligation as citizens to go out and explain what they need and what their work will mean.

I am 58 and I am already thinking about Alzheimer's disease and cancer. The fact that George Harrison has died and was my age makes mortality much more vivid. So, I have a vested interest in accelerating the rate of discovery and the application of that discovery. The largest single voting block is baby boomers, and they would all understand that argument. They may not understand plasma physics or the highest level of the human genome project. But they can surely understand the alternative between having Alzheimer's and not having it.

If you don't want Alzheimer's, you had better invest a lot more, not just in the National Institutes of Health (NIH) but also at the National Science Foundation (NSF) and a variety of other places, because the underlying core intellectual disciplines that make NIH possible all occur outside NIH. And most of the technology that NIH uses occurs outside of NIH. The argument has to be made by someone. If the scientific community refuses to make it, then you shouldn't be shocked that it's not made.

Let me suggest at a practical level what I think your assignments are once you've established a general vision. If you bring the four NBIC elements together into a converging pattern, you want to identify the missing gaps. What are the pieces that are missing? They may be enabling technologies, enabling networking, or joint projects.

Here again, I cite the great work done at the (Defense) Advanced Research Projects Agency ([D]ARPA). Scientists there consciously figured out the pieces that were missing to make computation easy to use and then began funding a series of centers of excellence that literally invented the modern world. You would not have gotten modern computing without ARPA, at least for another 30 years. Part of what they did that was so powerful was start with a general vision, figure out the pieces that were blocking the vision, and get them funded.

The predecessor to the Internet, ARPANET, wouldn't have occurred without two things: one was ARPA itself which had the funding, and the second was a vision that we should not be decapitated by a nuclear strike. People tend to forget that the capacity to surf on the Web in order to buy things is a direct function of our fear of nuclear war.

It helps to have the *vision* of very large breakthrough systems and some pretty long-term source of consistent funding. I've argued for the last three years that if we

are going to talk about global warming, we ought to have several billion dollars set aside for the kind of climatology capabilities that will be comparable to the international geophysical year, and it would really give us the knowledge to move things a long way beyond our current relative guesses. If you look at the difference between the public policy implications of the Kyoto agreement, in the $40 trillion range, and the amount of money you could plausibly invest if you had an opportunity-based atmospheric and climatological research program, the differences are just stunning. For far less than one percent of the cost we would in theory pay to meet Kyoto, you would have a database and a knowledge base on climatology that would be stunning.

That's outside current budgeting, because current budgeting is an incremental-increase pork barrel; it is not an intellectual exercise. I would argue that's a profound mistake. So, it's very important for you to figure out what are the large projects as a consequence of which we would be in a different league of capabilities. I would suggest, too, that both the international geophysical year and its stunning impact on the basic understanding of geology may be the most decisive change in paradigms in 20th century, at least in terms that everybody agreed it was right. I would also suggest to you the example of ARPANET, which ultimately enabled people to invent the World Wide Web. For today's purpose, take the NBIC convergence and work back to identify the large-scale projects that must be underway in order to create parallel kinds of capabilities.

I want to make further points about being unreasonable. Scientists really have an obligation to communicate in vivid, simple language the possibilities so that the President, the Vice-President and the various people who make budget decisions are forced to reject that future if they settle for lower budgets. It's really important that people understand what's at stake. It is my experience that consistently, politicians underestimate the potential of the future.

If we in fact had the right level of investment in aeronautics, we would not currently be competing with Airbus. We would be in two different worlds. Considering all the opportunities to dramatically change things out of nanoscale technology combined with large-scale computing, there's no doubt in my mind if we were willing to make a capital investment, we would create a next-generation aviation industry that would be stunningly different. It would be, literally, beyond competition by anything else on the planet. Our military advantage in Afghanistan compared with the 1979 Soviet capabilities isn't courage, knowledge of military history, or dramatically better organizational skills, but a direct function of science and technology. We need to say that, again and again.

I'll close with two thoughts. First, my minimum goal is to triple the NSF budget and then have comparable scalable increases. One of the major mistakes I made as Speaker of the House is that I committed to doubling NIH without including other parts of science. In retrospect, it was an enormous mistake. We should have proportionally carried the other scientific systems, many of which are smaller, to a substantial increase. I'm probably going to do penance for the next decade by arguing that we catch up. Second, in the media there is some talk that the Administration may offer cuts in science spending in order to get through this current budget. Let me just say this publicly as often as I can. That would be madness.

If we want this economy to grow, we have to be the leading scientific country in the world. If we want to be physically safe for the next 30 years, we have to be the leading scientific country in the world. If we want to be healthy as we age, we have to be the leading scientific country in the world. It would be literally madness to offer anything except an increase in science funding. And if anybody here is in the Administration, feel free to carry that back. I will say this publicly anywhere I can, and I will debate anyone in the Administration on this.

Congress finds billions for pork and much less for knowledge. That has to be said over and over. It's not that we don't have the money. You watch the pork spending between now and the time Congress leaves. They'll find plenty of appropriations money, if there is enough political pressure. Scientists and engineers have to learn to be at least as aggressive as corn farmers. A society that can make a profound case for ethanol can finance virtually anything, and I think we have to learn that this is reality.

Now, a lot of scientists feel above strongly advocating government funding for their work. Fine, then you won't get funded. Or you'll get funded because somebody else was a citizen. However, I don't accept the notion that scientists are above civic status, and that scientists don't have a citizen's duty to tell the truth as they understand it and argue passionately for the things they believe in.

I have this level of passion because I believe what you're doing is so profoundly real. It's real in the sense that there are people alive today that would have died of illnesses over the last week if it weren't for the last half-century of science. There are capabilities today that could allow us to create a fuel cell system in Afghanistan, as opposed to figuring out how to build a large central electric distribution system for a mountainous country with small villages. With satellite technology, we could literally create a cell phone capability for most of the country instantaneously as opposed to going back to copper.

I just visited in Romania ten days ago and saw a project that goes online December 2002 to provide 156 K mobile capability, and the Romanians think they'll be at the third generation of cellular phones at a 1.2 million capability by January of 2003. In effect, I think Romania may be the first country in the world that has a 100% footprint for the 1.2 meg cellphone business.

We ought to talk, not about re-creating 1973 Afghanistan, but about how to create a new, better, modern Afghanistan where the children have access to all kinds of information, knowledge, and capabilities. My guess is it will not be a function of money. You watch the amount of money we and the world community throw away in the next six years in Afghanistan, and the relatively modest progress it buys. Take the same number of dollars, and put them into a real connectivity, a real access to the best medicine, a real access to logical organization, and you will have a dramatically healthier country in a way that would improve the life of virtually every Afghan.

Real progress requires making the connection between science and human needs. Vannevar Bush's great effort in the Second World War was to take knowledge and match it up with the military requirements in a way that gave us radical advantages; the submarine war is a particularly good example. The key was bringing science into the public arena at the state of possibility. Most of the technological advances that were delivered in 1944 did not exist in 1940. They were invented in real-time in

places like MIT and brought to bear in some cases within a week or two of being invented.

I think we need that sense of urgency, and we need the sense of scale, because that's what Americans do well. We do very big things well, and we do things that are very urgent well. If they are not big enough and we bureaucratize them, we can often extend the length of time and money it takes by orders of magnitude. Thus, to be unreasonable in our planning can actually be quite realistic. We have entered a period I call The Age of Transitions, when science can achieve vast, positive improvements for the individual and the society, if we communicate the vision effectively.

The Age of Transitions: Converging Technologies

Overview

1. We are already experiencing the dramatic changes brought on by computers, communications, and the Internet. The combination of science and technology with entrepreneurs and venture capitalists has created a momentum of change which is extraordinary. Yet these changes will be overshadowed in the next 20 years by the emergence of an even bigger set of changes based on a combination of biology, information, and nanoscience (the science of objects at a billionth of a meter, from one to four hundred atoms in size). This new and as yet unappreciated wave of change will combine with the already remarkable pattern of change brought on by computers, communication, and the Internet to create a continuing series of new breakthroughs, resulting in new goods and services. We will be constantly in transition as each new idea is succeeded by an even better one. This will be an Age of Transitions, and it will last for at least a half-century.
2. In the Age of Transitions, the ways we acquire goods and services are rapidly evolving in the private sector and in our personal lives. Government and bureaucracy are changing at a dramatically slower rate, and the gaps between the potential goods and services, productivity, efficiencies, and conveniences being created and the traditional behaviors of government and bureaucracies are getting wider.
3. The language of politics and government is increasingly isolated from the language of everyday life. Political elites increasingly speak a language that is a separate dialect from the words people use to describe their daily lives and their daily concerns. The result in part is that the American people increasingly tune out politics.
4. Eventually a political movement will develop a program of change for government that will provide greater goods and services at lower and lower costs. When that movement can explain its new solutions in the language of everyday life, it will gain a decisive majority as people opt for better lives through better solutions by bringing government into conformity with the entrepreneurial systems they are experiencing in the private sector.
5. Understanding the Age of Transitions is a very complex process and requires thought and planning. It involves applying principles to create better solutions for delivery of government goods and services and developing and communicating a program in the language of everyday life, so that people

hear it and believe it despite the clutter and distractions of the traditional language of politics and government.

Introduction

We are living through two tremendous patterns of scientific-technological change: an overlapping of a computer-communications revolution and a nanotechnology-biology-information revolution. Each alone would be powerful; combined, the two patterns guarantee that we will be in constant transition as one breakthrough or innovation follows another.

Those who study, understand, and invest in these patterns will live dramatically better than those who ignore them. Nations that focus their systems of learning, healthcare, economic growth, and national security on these changes will have healthier, more knowledgeable people in more productive jobs creating greater wealth and prosperity and living in greater safety through more modern, more powerful intelligence and defense capabilities.

Those countries that ignore these patterns of change will fall further behind and find themselves weaker, poorer, and more vulnerable than their wiser, more change-oriented neighbors.

The United States will have to continue to invest in new science and to adapt its systems of health, learning, and national security to these patterns of change if we want to continue to lead the world in prosperity, quality of life, and military-intelligence capabilities.

At a minimum, we need to double the federal research budget at all levels, reform science and math learning decisively, and to modernize our systems of health, learning, and government administration.

Periods of transition are periods of dramatic cost crashes. We should be able to use the new patterns of change to produce greater health and greater learning at lower cost. Government administration can be more effective at lower cost. Our national security will experience similar crashes in cost.

This combination of better outcomes at lower cost will not be produced by liberal or conservative ideology. It will be produced by the systematic study of the new patterns and the use of new innovations and new technologies.

Simply Be a More Powerful Industrial Era

Computing is a key element in this revolution. The numbers are stunning. According to Professor James Meindl, the chairman of the Georgia Tech Microelectronics Department, the first computer built with a transistor was Tradic in 1955, and it had only 800 transistors. The Pentium II chip has 7,500,000 transistors. In the next year or so, an experimental chip will be built with one billion transistors. Within 15 to 20 years, there will be a chip with one trillion transistors. However that scale of change is graphed, it is enormous, and its implications are huge. It is estimated that we are only one-fifth of the way into developing the computer revolution.

Yet focusing only on computer power understates the scale of change. Communications capabilities are going to continue to expand dramatically, and that may have as big an impact as computing power. Today, most homes get Internet access at 28,000 to 56,000 bits per second. Within a few years, a combination of new technologies for compressing information (allowing you to get more done in a

given capacity) with bigger capacity (fiberoptic and cable) and entirely new approaches (such as satellite direct broadcast for the Internet) may move household access up to at least six million bits per second and some believe we may reach the 110 million bits needed for uncompressed motion pictures. Combined with the development of high definition television and virtual systems, an amazing range of opportunities will open up. This may be expanded even further by the continuing development of the cell phone into a universal utility with voice, Internet, credit card, and television applications all in one portable hand-held phone.

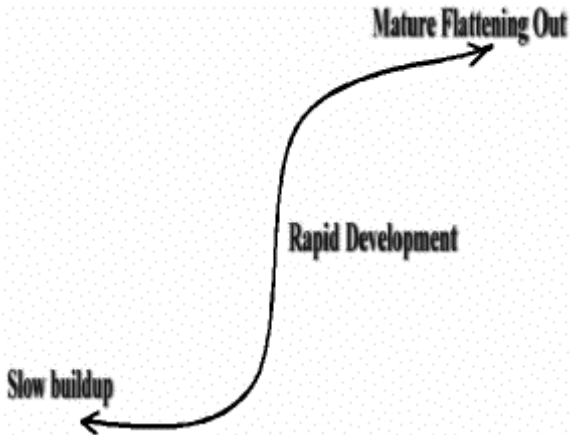

Figure A.1. The S-curve of technological change.

The S-curve of Technological Change

The communications-computer revolution and the earlier Industrial Revolution are both examples of the concept of an "S"-curve. The S-curve depicts the evolution of technological change. Science and technology begin to accelerate slowly, and then as knowledge and experience accumulates, they grow much more rapidly. Finally, once the field has matured, the rate of change levels off. The resulting pattern looks like an S. An overall S-curve is made up of thousands of smaller breakthroughs that create many small S-curves of technological growth.

The Two S-Curves of the Age of Transitions

We are starting to live through two patterns of change. The first is the enormous computer and communications revolution described above. The second, only now beginning to rise, is the combination of the nanotechnology-biology-information revolution. These two S curves will overlap. It is the overlapping period that we are just beginning to enter, and it is that period that I believe

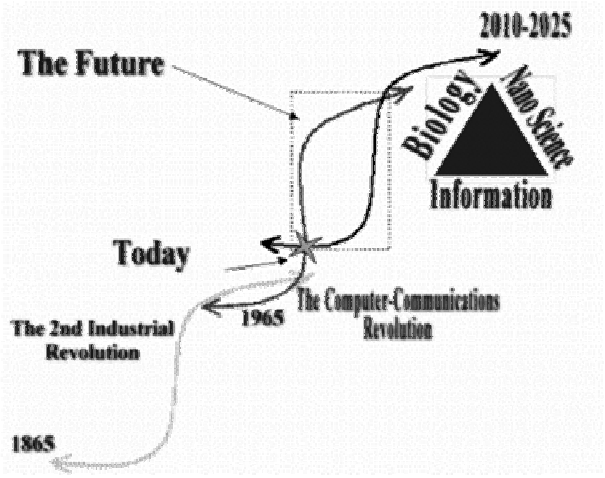

Figure A.2. The Age of Transitions.

will be an Age of Transitions.

The Nano World, Biology, and Information as the Next Wave of Change

Focusing on computers and communications is only the first step toward understanding the Age of Transitions. While we are still in the early stages of the computer-communications pattern of change, we are already beginning to see a new, even more powerful pattern of change that will be built on a synergistic interaction among three different areas: the nano world, biology, and information.

The nano world may be the most powerful new area of understanding. "Nano" is the space measuring between one atom and about 400 atoms. It is the space in which quantum behavior begins to replace the Newtonian physics you and I are used to. The word "nano" means one-billionth and is usually used in reference to a nanosecond (one billionth of a second) or a nanometer (one billionth of a meter). In this world of atoms and molecules, new tools and new techniques are enabling scientists to create entirely new approaches to manufacturing and healthcare. Nanotechnology "grows" materials by adding the right atoms and molecules. Ubiquitous nanotechnology use is probably 20 years away, but it may be at least as powerful as space or computing in its implications for new tools and new capabilities.

The nano world also includes a series of materials technology breakthroughs that will continue to change the way we build things, how much they weigh, and how much stress and punishment they can take. For example, it may be possible to grow carbon storage tubes so small that hydrogen could be safely stored without refrigeration, thus enabling the creation of a hydrogen fuel cell technology, with dramatic implications for the economy and the environment. These new materials may make possible a one-hour flight from New York to Tokyo, an ultra-lightweight car, and a host of other possibilities. Imagine a carbon tube 100 times as strong as steel and only one-sixth as heavy. It has already been grown in the NASA Ames Laboratory. This approach to manufacturing will save energy, conserve our raw materials, eliminate waste products, and produce a dramatically healthier environment. The implications for the advancement of environmentalism and the irrelevancy of oil prices alone are impressive.

The nano world makes possible the ability to grow molecular "helpers" (not really "tools" because they may be organic and be grown rather than built). We may be able to develop anti-cancer molecules that penetrate cells without damaging them and hunt cancer at its earliest development. Imagine drinking with your normal orange juice 3,000,000 molecular rotor rooters to clean out your arteries without an operation.

The nano world opens up our understanding of biology, and biology teaches us about the nano world because virtually all biological activities take place at a molecular level. Thus, our growing capabilities in nano tools will dramatically expand our understanding of biology. Our growing knowledge about molecular biology will expand our understanding of the nano world.

Beyond the implications of biology for the nano world, in the next decade, the Human Genome Project will teach us more about humans than our total knowledge to this point. The development of new technologies (largely a function of physics and mathematics) will increase our understanding of the human brain in ways

previously unimaginable. From Alzheimer's to Parkinson's to schizophrenia, there will be virtually no aspect of our understanding of the human brain and nervous system that cannot be transformed in the next two decades.

We are on the verge of creating intelligent synthetic environments that will revolutionize how medical institutions both educate and plan. It will be possible to practice a complicated, dangerous operation many times in a synthetic world with feel, smell, appearance, and sound, that are all precisely the same as the real operation. The flight and combat simulators of today are incredibly better than the sand tables and paper targets of forty years ago. An intelligent, synthetic environment will be an even bigger breakthrough from our current capabilities. It will be possible to design a building or an organization in the synthetic world before deciding whether to actually build it. The opportunities for education will be unending.

Finally, the information revolution (computers and communications) will give us vastly better capabilities to deal with the nano world and with biology.

It is the synergistic effect of these three systems (the nano world, biology, and information) that will lead to an explosion of new knowledge and new capabilities and create intersecting S-curves. We will simultaneously experience the computer/communications revolution and the nano/biology/information revolution. These two curves will create an Age of Transitions.

This rest of this paper attempts to outline the scale of change being brought about by the Age of Transitions, the principles that underlie those changes, and how to apply those principles in a strategic process that could lead to a governing majority.

Politics and Government in the Age of Transitions

In the foreseeable future, we will be inundated with new inventions, new discoveries, new startups, and new entrepreneurs. These will create new goods and services. The e-customer will become the e-patient and the e-voter. As expectations change, the process of politics and government will change. People's lives will be more complex and inevitably overwhelming. Keeping up with the changes that affect them and their loved ones exhausts most people. They focus most of their time and energy on the tasks of everyday life. In the future, when they achieve success in their daily tasks, people will turn to the new goods and services, the new job and investment opportunities, and the new ideas inherent in the entrepreneurial creativity of the Age of Transitions. No individual and no country will fully understand all of the changes as they occur or be able to adapt to them flawlessly during this time. On the other hand, there will be a large premium placed on individuals, companies, and countries that are able to learn and adjust more rapidly.

The political party or movement that can combine these three zones into one national dialogue will have an enormous advantage, both in offering better goods and services, and in attracting the support of most Americans.

The new products and services created by the Age of Transitions are creating vast opportunities for improving everyday life. The government has an opportunity to use these new principles to develop far more effective and appropriate government services. Politicians have the chance to explain these opportunities in a language most citizens can understand and to offer a better future, with greater quality of life, by absorbing the Age of Transitions into government and politics.

The average citizen needs to have political leadership that understands the scale of change we are undergoing, that has the ability to offer some effective guidance about how to reorganize daily life, and that simultaneously has the ability to reorganize the government that affects so much of our daily life. Inevitably, the Age of Transitions will overwhelm and exhaust people. Only after they have dealt with their own lives do they turn to the world of politics and government.

When we look at politics, we are discouraged and in some cases repulsed by the conflict-oriented political environment; the nitpicking, cynical nature of the commentaries; and the micromanaged, overly detailed style of political-insider coverage. The more Americans focus on the common sense and the cooperative effort required for their own lives, and the more they focus on the excitement and the wealth-creating and opportunity-creating nature of the entrepreneurial world, the more they reject politics and government as an area of useful interest.

Not only do politics and government seem more destructive and conflict oriented, but the language of politics seems increasingly archaic and the ideas increasingly trivial or irrelevant. People who live their lives with the speed, accuracy, and convenience of automatic teller machines (ATMs) giving them cash at any time in any city, cell phones that work easily virtually everywhere, the ease of shopping on the Web and staying in touch through email, will find the bureaucratic, interest-group-focused, and arcane nature of political dialogue and government policy to be painfully outmoded. Politicians' efforts to popularize the obsolete are seen as increasingly irrelevant and are therefore ignored.

This phenomenon helps explain the January 2000 poll in which 81 percent of Americans said that they had not read about the presidential campaign in the last 24 hours, 89 percent said that they had not thought about a presidential candidate in the same period, and 74 percent said that they did not have a candidate for president (up 10 percent from the previous November).

The average voter's sense of distance from politics is felt even more strongly by the entrepreneurial and scientific groups that are inventing the future. They find the

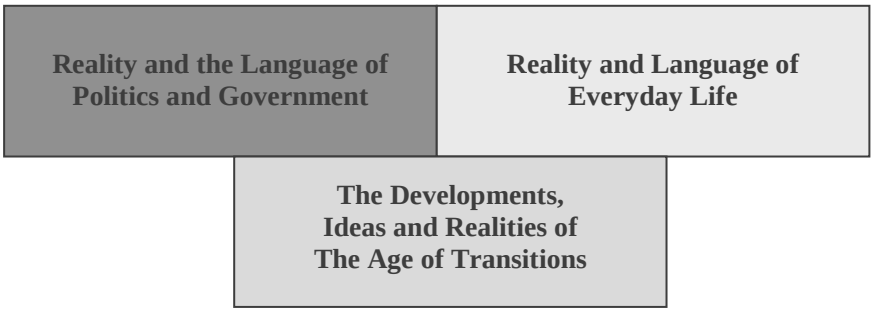

Figure A.3. Zones of social reality in the Age of Transitions.

difference between their intensely concentrated, creative, and positive focus of energy and the negative, bickering nature of politics especially alienating, so they focus on their own creativity and generally stay aloof from politics unless a specific interest is threatened or a specific issue arouses their interest.

Projects that focus on voter participation miss the nature of a deliberate avoidance by voters of politics. In some ways, this is a reversion to an American norm prior to the Great Depression and World War II. For most of American history, people focused their energies on their own lives and their immediate communities. The national government (and often even the state government) seemed distant and irrelevant. This was the world of very limited government desired by Jefferson and described by Tocqueville in *Democracy in America*. With the exception of the Civil War, this was the operating model from 1776 until 1930. Then the Depression led to the rise of Big Government, the World War II led to even bigger government, and the Cold War sustained a focus on Washington. When there was a real danger of nuclear war and the continuing crisis threatened the survival of freedom, it was natural for the president to be the central figure in America and for attention to focus on Washington. With the collapse of the Soviet Union, there has been a gradual shift of power and attention from Washington and back to the state and local communities. There has been a steady decline in popular attention paid to national politics.

When Republicans designed a positive campaign of big ideas in the 1994 Contract With America, some nine million additional voters turned out (the largest off-year, one-party increase in history). When Jesse Ventura offered a real alternative (at least in style) in 1998, younger voters turned out in record numbers. The voter as a customer tells the political-governmental system something profound by his or her indifference. The political leadership is simply failing to produce a large enough set of solutions in a lay language worth the time, attention, and focus of increasingly busy American citizens.

After a year of traveling around 23 states in America and spending time with entrepreneurs, scientists, and venture capitalists, I am increasingly convinced that the American voters are right.

Let us imagine a world of 1870 in which the private sector had completed the transcontinental railroad and the telegraph but the political-governmental elites had decided that they would operate by the rules of the Pony Express and the stagecoach. In private life and business life, you could telegraph from Washington to San Francisco in a minute and ship a cargo by rail in seven days. However, in political-governmental life, you had to send written messages by pony express that took two weeks and cargo by stagecoach that took two months. The growing gap between the two capabilities would have driven you to despair about politics and government as being destructive, anachronistic systems.

Similarly, imagine that in 1900 a Washington Conference on Transportation Improvement had been created, but the political-governmental elite had ruled that the only topic would be the future of the horseshoe and busied themselves with a brass versus iron horseshoe debate. Henry Ford's efforts to create a mass-produced automobile would have been ruled impractical and irrelevant. The Wright brothers' effort to create an airplane would have been derided as an absurd fantasy. After all, neither clearly stood on either the brass or the iron side of the debate. Yet which

would do more to change transportation over the next two decades: the political-governmental power structure of Washington or the unknown visionaries experimenting without government grants and without recognition by the elites?

Consider just one example of the extraordinary and growing gap between the opportunities of the Age of Transitions and the reactionary nature of current government systems. The next time you use your ATM card, consider that you are sending a code over the Internet to approve taking cash out of your checking account. It can be done on a 24 hours a day, seven days a week anywhere in the country. Compare that speed, efficiency, security, and accuracy with the paper-dominated, fraud- and waste-ridden Healthcare Financing Administration (HCFA) with its 133,000 pages of regulations (more pages than the tax code). As a symbol of a hopelessly archaic model of bureaucracy there are few better examples than HCFA.

This growing gap between the realities and language of private life and the Age of Transitions, on the one hand, and the increasingly obsolete language and timid proposals of the political governmental system, on the other hand, convinces more and more voters to ignore politics and focus on their own lives and on surviving the transitions.

This is precisely the pattern described by Norman Nie and colleagues in *The Changing American Voter* (1979). They described a pool of latent voters who in the 1920s found nothing in the political dialogue to interest them. These citizens simply stayed out of the process as long as it stayed out of their lives. The Depression did not mobilize them. They sat out the 1932 election. Only when the New Deal policies of Franklin Delano Roosevelt penetrated their lives did they become involved. In 1936, Alf Landon, the Republican nominee, actually received a million more votes than Herbert Hoover had gotten in 1932. However, FDR received seven million more votes than he had gotten in his first election. It was this massive increase in participation that made the polls inaccurate and created the Democratic majority, which in many ways survived until the 1994 election. The Republican victory of 1994 drew nine million additional voters over its 1990 results by using bold promises in a positive campaign to engage people who had been turned off by politics.

A similar opportunity awaits the first political party and political leader to make sense of the possibilities being created by the Age of Transitions and to develop both a language and a set of bold proposals that make sense to average Americans in the context of their own lives and experiences.

This paper should be seen as the beginning of a process rather than as a set of answers. Political-governmental leaders need to integrate the changes of the Age of Transitions with the opportunities these changes create to improve people's lives, develop the changes in government necessary to accelerate those improvements, and explain the Age of Transitions era — and the policies it requires — in the language of everyday life, so that people will understand why it is worth their while to be involved in politics and subsequently improve their own lives. Getting this done will take a lot of people experimenting and attempting to meet the challenge for a number of years. That is how the Jeffersonians, the Jacksonians, the early Republicans, the Progressives, the New Dealers, and the Reagan conservatives succeeded. Each, over time, created a new understanding of America at an historic

moment. We aren't any smarter, and we won't get it done any faster; however, the time to start is now, and the way to start is to clearly understand the scale of the opportunity and the principles that make it work.

Characteristics of an Age of Transitions

Thirty-six years after Boulding's first explanation of the coming change, and thirty-one years after Drucker explained how to think about discontinuity, some key characteristics have emerged. This section outlines 18 characteristics and gives examples of ways political and governmental leaders can help develop the appropriate policies for the Age of Transitions. It should first be noted that there is an overarching general rule: assume there are more changes coming.

It is clear that more scientists, engineers, and entrepreneurs are active today than in all of previous human history. Venture capitalists are developing powerful models for investing in and growing startup companies. In the process, they are acquiring more and more capital as the markets shift away from the smokestack industries and toward new models. It is also clear that there is a growing world market in which more entrepreneurs of more nationalities are competing for more customers than ever in human history.

All this growing momentum of change simply means that no understanding, no reform, no principle will be guaranteed to last for very long. Just as we get good at one thing or come to understand one principle, it will be challenged by an emerging new idea or achievement from a direction we haven't even considered.

Within that humbling sense that the change is so large that we will never really know in our lifetime the full analysis of this process, here are 18 powerful characteristics for developing government policy and politics in the Age of Transitions:

1. **Costs will crash.** A major pattern will be a continuing, and in many cases steep, decline in cost. An ATM is dramatically cheaper than a bank teller. A direct-dial phone call is much less expensive than an operator-assisted call. My brother used Priceline.com and received four airline tickets for his family for the price of one regular ticket. We have not even begun to realize how much costs will decline, even in the fields of health and healthcare, education and learning, defense procurement, and government administration. We also have not yet learned to think in terms of purchasing power instead of salary. Yet the pattern is likely to be a huge change in both purchasing power and behavior for both citizens and government. Those who are aggressive and alert will find remarkable savings by moving to the optimum cost crashes faster than anyone else. As a result, they will dramatically expand their purchasing power.
2. **Systems will be customer-centered and personalized.** Customers of Amazon.com and other systems already can look up precisely the books or movies that interest them, and after a while, the company is able to project their interests and alert them to similar products in their inventory. Consumers can consider personal Social Security Plus accounts who already have personal Roth IRAs and 401Ks. Individuals can consider purchasing personal learning and personal health systems just as they purchase electronic airline tickets on the Internet. Anything that is not personalized

and responsive to changing individual needs will rapidly be replaced by something that is.

3. **24-7 will be the world of the future. .** Customer access 24 hours a day, 7 days a week, will become the standard of the future. ATMs symbolize this emerging customer convenience standard, providing cash to card-holders any day, round the clock. Yet today's schools combine an agricultural-era nine- or ten-month school year (including the summer off for harvesting) with an industrial era 50-minute class, with a "foreman" at the front of the room facing a class of "workers" in a factory-style school day, in a Monday-to-Friday work week. Learning in the future will be embedded in the computer and on the Internet and will be available on demand with a great deal of customization for each learner. Similarly, government offices will have to shift to meeting their constituents' needs at their convenience rather than demanding that the constituents make themselves available at the bureaucrat's convenience. These are big changes, and they are unavoidable given the emerging technologies and the e-customer culture that is evolving.
4. **Convenience will be a high value. .** As customers get used to one-click shopping (note the shopping cart approach on Amazon), they will demand similar convenience from government. People will increasingly order products and services to be delivered to their homes at their convenience. They will initially pay a premium for this convenience, but over time they will conclude that it is a basic requirement of any business that they deal with, and costs will go down. After a while, e-customers will begin to carry these attitudes into their relationship with bureaucracy, and as e-voters they will favor politicians who work to make their lives easier (i.e., more convenient).
5. **Convergence of technologies will increase convenience, expand capabilities, and lower costs. .** The various computation and communication technologies will rapidly converge with cell phones, computers, land-lines, mobile systems, satellite capabilities, and cable, all converging into a unified system of capabilities that will dramatically expand both capabilities and convenience.
6. **Processes will be expert system-empowered. .** When you look up an airline reservation on the Internet, you are dealing with an expert system. In virtually all Internet shopping you are actually interacting with such a system. The great increase in capability for dealing with individual sales and individual tastes is a function of the growing capacity of expert systems. These capabilities will revolutionize health, learning, and government once they are used as frequently as they currently are in the commercial world. If it can be codified and standardized, it should be done by an expert system rather than a person: that is a simple rule to apply to every government activity.
7. **Middlemen will disappear.** This is one of the most powerful rules of the Age of Transitions. In the commercial world, where competition and profit margins force change, it is clear that customers are served more and more from very flat hierarchies, with very few people in the middle. In the protected guilds (medicine, teaching, law, and any group that can use its

political power to slow change) and in government structures, there are still very large numbers of middlemen. This will be one of the most profitable areas for political-governmental leaders to explore. In the Age of Transitions, the customer should be foremost, and every unnecessary layer should be eliminated to create a more agile, more rapidly changing, more customer-centered, and less expensive system.

8. **Changes can come from anywhere. .** The record of the last thirty years has been of a growing shift toward new ideas coming from new places. Anyone can have a good idea, and the key is to focus on the power of the idea rather than the pedigree of the inventor. This directly challenges some of the peer review assumptions of the scientific community, much of the screening for consultants used by government, much of the credentialing done by education and medicine, and much of the contractor certification done by government. This principle requires us to look very widely for the newest idea, the newest product, and the newest service, and it requires testing by trial and error more than by credentialing or traditional assumptions.

9. **Resources will shift from opportunity to opportunity. .** One of the most powerful engines driving the American economy has been the rise of an entrepreneurial venture capitalism that moves investments to new opportunities and grows those opportunities better than any other economy in the world. There is as yet no comparable government capacity to shift resources to new start-ups and to empower governmental entrepreneurs. There are countless efforts to reform and modernize bureaucracies, but that is exactly the wrong strategy. Venture capitalists very seldom put new money into old corporate bureaucracies. Even many established corporations are learning to create their own startups because they have to house new ideas and new people in new structures if they are really to get the big breakthroughs. We need a doctrine for a venture capitalist-entrepreneurial model of government that includes learning, health, and defense.

10. **The rapid introduction of better, less expensive products will lead to continual replacement. .** Goods and services will take on a temporary nature as their replacements literally push them out of the door. The process of new, more capable, and less expensive goods and services, and in some cases, revolutionary replacements that change everything (as Xerox did to the mimeograph, and as the fax machine, e-mail, and PC have done) will lead to a sense of conditional existence and temporary leasing that will change our sense of ownership.

11. **The focus will be on success. .** Entrepreneurs and venture capitalists have a surprisingly high tolerance for intelligent failure. They praise those who take risks, even if they fail, over those who avoid risks, even if they avoid failure. To innovate and change at the rate the Age of Transitions requires, government and politicians have to shift their attitudes dramatically. (It would help if the political news media joined them in this.) Today it is far more dangerous for a bureaucrat to take a risk than it is to do nothing. Today the system rewards people (with retirement and noncontroversy) for serving their time in government. There are virtually no rewards for taking the risks and sometimes failing, sometimes succeeding. Yet in all the areas of science,

technology, and entrepreneurship, the great breakthroughs often involve a series of failures. (Consider Edison's thousands of failed experiments in inventing the electric light and how they would have appeared in a congressional hearing or a news media expose.) Setting a tone that supports trying and rewards success while tolerating intelligent failure would do a great deal to set the stage for a modernized government.

12. **Venture capitalists and entrepreneurs will focus on opportunities. .** This is similar to focusing on success but refers to the zone in which energy and resources are invested. It is the nature of politics and government to focus on problems (schools that fail, hospitals that are too expensive, people who live in poverty) when the real breakthroughs come from focusing on opportunities (new models of learning that work, new approaches to health and healthcare that lower the cost of hospitals, ways to get people to work so that they are no longer in poverty). Venture capitalists are very good at shifting their attention away from problem zones toward opportunity zones. Politicians and the political news media tend to do the opposite. Yet the great opportunities for change and progress are in the opportunities rather than the problems.
13. **Real breakthroughs will create new products and new expectations. .** Before Disney World existed, it would have been hard to imagine how many millions would travel to Orlando. Before the Super Bowl became a cultural event, it was hard to imagine how much of the country would stop for an entire evening. Before faxes, we did not need them, and before e-mail, no one knew how helpful it would be. One of the key differences between the public and private sector is this speed of accepting new products and creating new expectations. The public sector tends to insist on using the new to prop up the old. For two generations we have tried to get the computer into the classroom with minimal results. That's because it is backward. The key is to get the classroom into the computer and the computer to the child's home, so that learning becomes personal and 24/7. Doctors still resist the information technologies that will revolutionize health and healthcare and that will lower administrative costs and decrease unnecessary deaths and illnesses dramatically. In the private sector, competition and the customer force change. In government and government-protected guilds, the innovations are distorted to prop up the old, and the public (that is the customer) suffers from more expensive and less effective goods and services.
14. **Speed matters: new things will need to get done quickly. .** There is a phrase in the Internet industry, "launch and learn," which captures the entrepreneurial sense of getting things done quickly and learning while doing so. One Silicon Valley entrepreneur noted he had moved back from the East because he could get things done in the same number of days in California as the number of months it would have taken where he had been. Moving quickly produces more mistakes, but it also produces a real learning that only occurs by trying things out. The sheer volume of activity and the speed of correcting mistakes as fast as they are discovered allows a "launch and learn" system to grow dramatically faster than a "study and launch" system. This explains one of the major differences between the venture capitalist-entrepreneurial world and the world of traditional corporate bureaucracies.

Since governments tend to study and study without ever launching anything truly new, it is clear how the gap widens between the public and private sectors in an Age of Transitions. Today it takes longer for a presidential appointee to be cleared by the White House and approved by the Senate than it takes to launch a startup company in Silicon Valley.

15. **Start small but dream big. .** Venture capital and entrepreneurship are about baby businesses rather than small businesses. Venture capitalists know that in a period of dramatic change, it is the occasional home run rather than a large number of singles that really make the difference. The result is that venture capitalists examine every investment with a focus on its upside. If it does not have a big enough growth potential, it is not worth the time and energy to make the investment. Government tends to make large, risk-averse investments in relatively small, controllable changes. This is almost the exact opposite of the venture capital-entrepreneurial model. The question to ask is, "If this succeeds, how big will the difference be, and if the difference isn't very substantial, we need to keep looking for a more powerful proposal."
16. **Business-to-business is the first big profit opportunity. .** While most of the attention in the Internet market is paid to sales to the final customer, the fact is that that market is still relatively small and relatively unprofitable. However, there is no question that Internet-based systems such as Siebel and Intelisys are creating business-to-business opportunities that will dramatically lower the cost of doing business. Every government, at every level, should be rationalizing its purchasing system and moving on to the net to eliminate all paper purchasing. The savings in this area alone could be in the 20 percent to 30 percent range for most governments. The opportunities for a paperless system in health and healthcare could lead to a crash in costs rather than a worry about rising costs.
17. **Applying quality and lean thinking can save enormous amounts.** Whether it is the earlier model of quality espoused by Edwards Deming, or the more recent concept of lean thinking advocated by James Womack and Daniel Jones, it is clear that there is an existing model for systematically thinking through production and value to create more profitable, less expensive approaches. The companies that have really followed this model have had remarkable success in producing better products at lower expense, yet it is almost never used by people who want to rethink government.
18. **Partnering will be essential.** No company or government can possibly understand all the changes in an Age of Transitions. Furthermore, new ideas will emerge with great speed. It is more profitable to partner than to try to build in-house expertise. It allows everyone to focus on what they do best while working as a team on a common goal. This system is prohibited throughout most of government, and yet it is the dominant organizing system of the current era of startups. As government bureaucracies fall further and further behind the most dynamic of the startups (in part because civil service salaries cannot compete with stock options for the best talent), it will become more and more important to develop new mechanisms for government-private partnering.

These initial principles give a flavor of how big the change will be and of the kind of questions a political-governmental leader should ask in designing a program for the Age of Transitions. These principles and questions can be refined, expanded, and improved, but they at least let leaders start the process of identifying how different the emerging system will be from the bureaucratic-industrial system that is at the heart of contemporary government.

The Principles of Political-Governmental Success in an Age of Transitions

In the Age of Transitions, the sheer volume of new products, new information, and new opportunities will keep people so limited in spare time that any real breakthrough in government and politics will have to meet several key criteria:

1. **Personal.** It has to involve a change that occurs in individual people's lives in order for them to think it is worth their while, because it will affect them directly. Only a major crisis such as a steep recession or a major war will bring people back to the language of politics. In the absence of such a national crisis, political leaders will not be able to attract people into the zone of government and politics unless they use the new technologies and new opportunities of the Age of Transitions to offer solutions that will dramatically improve people's lives.
2. **Big Ideas.** The changes offered have to be large enough to be worth the time and effort of participation. People have to convinced that their lives or their families' lives will be affected significantly by the proposals, or they will simply nod pleasantly at the little ideas but will do nothing to get them implemented.
3. **Common Language.** New solutions have to be explained in the language of everyday life because people will simply refuse to listen to the traditional language of political and governmental elites. People have become so tired of the bickering, the conflict, and the reactionary obsolete patterns of traditional politics that they turn off the minute they hear them. New solutions require new words, and the words have to grow out of the daily lives of people rather than out of the glossary of intellectual elites or the slogans of political consultants.
4. **Practical.** The successful politics of the Age of Transitions will almost certainly be pragmatic and practical rather than ideological and theoretical. People are going to be so busy and so harried that their first question is going to be "will it work?" They will favor conservative ideas that they think will work, and they will favor big government ideas that they think will work. Their first test will be, "Will my family and I be better off?" Their second test will be, "Can they really deliver and make this work?' Only when a solution passes these two tests will it be supported by a majority of people. Note that both questions are pragmatic; neither is theoretical or ideological.
5. **Positive.** The successful politicians of the Age of Transitions will devote 80 percent of their time to the development and communication of large positive solutions in the language of everyday life and the gathering of grassroots coalitions and activists to support their ideas. They will never spend more than 20 percent of their effort on describing the negative characteristics of their opponents. When they do describe the destructive side of their

opponents, it will be almost entirely in terms of the costs to Americans of the reactionary forces blocking the new solutions and the better programs (study FDR's 1936 and 1940 campaigns for models of this lifestyle definition of the two sides: the helpful and the harmful. FDR was tough on offense, but more importantly, he cast the opposition in terms of how they hurt the lives of ordinary people.)

6. **Electronic.** The successful large, personal, positive, practical movement of the Age of Transitions will be organized on the Internet and will be interactive. Citizens will have a stake in the movement and an ability to offer ideas and participate creatively in ways no one has ever managed before. The participatory explosion of the 1992 Perot campaign, in which tens of thousands of volunteers organized themselves, and the Internet-based activism of the closing weeks of the 1998 Ventura campaign are forerunners of an interactive, Internet-based movement in the Age of Transitions. None has yet occurred on a sustainable basis, for two reasons:
   a) First, no one has come up with a believable solution big enough to justify the outpouring of energy beyond brief, personality-focused campaign spasms lasting weeks or a few months.
   b) Second, no one has mastered the challenge of building a citizen-focused genuinely interactive system that allows people to get information when they want it, offer ideas in an effective feedback loop, and organize themselves to be effective in a reasonably efficient and convenient manner. When the size of the solution and the sophistication of the system come together, we will have a new model of politics and government that will be as defining as the thirty-second commercial and the phone bank have been.

The Political Challenge for the Coming Decade in America

For change to be successful, it is essential that we sincerely and aggressively communicate in ways that are inclusive, not exclusive. Our political system cannot sustain effectiveness without being inclusive. There are two principle reasons this strategy must be pursued:

1. A majority in the Age of Transitions will be inclusive. The American people have reached a decisive conclusion that they want a unified nation with no discrimination, no bias, and no exclusions based on race, religion, sex, or disability. A party or movement that is seen as exclusionary will be a permanent minority. The majority political party in the Age of Transitions will have solutions that improve the lives of the vast majority of Americans and will make special efforts to recruit activists from minority groups, to communicate in minority media, and to work with existing institutions in minority communities. For Republicans, this will mean a major effort to attract and work with every American of every background. Only a visibly, aggressively inclusive Republican Party will be capable of being a majority in the Age of Transitions.
2. The ultimate arbiter of majority status in the next generation will be the Hispanic community. The numbers are simple and indisputable. If Hispanics become Republican, the Republican Party is the majority party for the

foreseeable future; if Hispanics become Democrat, the Republican Party is the minority party for at least a generation. On issues and values, Hispanics are very open to the Republican Party. On historic affinity and networking among professional politicians and activist groups, Democrats have an edge among Hispanics. There should be no higher priority for American politicians than reaching out to and incorporating Hispanics at every level in every state. George W. Bush, when he was governor of Texas, and Governor Jeb Bush have proven that Republicans can be effectively inclusive and create a working partnership with Hispanics. Every elected official and every candidate should follow their example.

Conclusion

These are examples of the kind of large changes that are going to be made available and even practical by the Age of Transitions. The movement or political party that first understands the potential of the Age of Transitions, develops an understanding of the operating principles of that Age, applies them to creating better solutions, and then communicates those solutions in the language of everyday life will have a great advantage in seeking to become a stable, governing majority.

This paper outlines the beginning of a process as big as the Progressive Era or the rise of Jacksonian Democracy, the Republicans, the New Deal, or the conservative movement of Goldwater and Reagan. This paper outlines the beginning of a journey, not its conclusion. It will take a lot of people learning, experimenting, and exploring over the next decade to truly create the inevitable breakthrough.

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ZONE OF CONVERGENCE BETWEEN BIO/INFO/NANO TECHNOLOGIES: NASA'S NANOTECHNOLOGY INITIATIVE

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NASA's mission encompasses space and Earth science, fundamental biological and physical research (BPR), human exploration and development of space (HEDS), and a responsibility for providing advanced technologies for aeronautics and space systems. In space science, agency missions are providing deeper insight into the

evolution of the solar system and its relationship to Earth; structure and evolution of the universe at large; and both the origins and extent of life throughout the cosmos. In Earth science, a fundamental focus is to provide, through observations and models, the role of the physical, chemical, and biological processes in long-term climate change as well as push the prediction capability of short-term weather. In addition, NASA's challenge is to understand the biosphere and its evolution and future health in the face of change wrought by humankind.

The goal of NASA for BPR is to conduct research to enable safe and productive human habitation of space as well as to use the space environment as a laboratory to test the fundamental principals of biology, physics, and chemistry. For HEDS, a long-term presence in low Earth orbit is being accomplished with the space station. In the longer term, humans will venture beyond low earth orbit, probably first to explore Mars, following a path blazed by robotic systems.

A critical element of science missions and HEDS is safe and affordable access to space and dramatically reduced transit times for in-space transportation systems. In pursuance of this mission, NASA needs tools and technologies that must push the present state of the art. NASA spacecraft must function safely and reliably, on their own, far from Earth, in the extremely harsh space environment in terms of radiation and temperature variance coupled with the absence of gravity. This places demands on NASA technologies that are highly unique to the Agency. NASA's aeronautics goals are focused on developing technology to support new generations of aircraft that are safer, quieter, more fuel efficient, environmentally cleaner, and more economical than today's aircraft; as well as on technology to enable new approaches to air systems management that can greatly expand the capacity of our air space and make it even safer than it is today.

Virtually all of NASA's vision for the future of space exploration — and new generations of aircraft — is dependent upon mass, power requirements, and the size and intelligence of components that make up air and space vehicles, spacecraft, and rovers. Dramatic increases in the strength-to-weight ratio of structural materials offers the potential to reduce launch and flight costs to acceptable levels. Such structural materials can also lead to increases in payload and range for aircraft, which can translate into U.S. dominance of the world marketplace. Packing densities and power consumption are absolutely critical to realizing the sophisticated on-board computing capability required for such stressing applications as autonomous exploration of Europa for evidence of simple life forms or their precursors. The integration of sensing, computing, and wireless transmission will enable true health management of reusable launch vehicles and aircraft of the future.

To do this, NASA aircraft and space systems will have to be much more capable than they are today. They will have to have the characteristics of autonomy to "think for themselves": they will need self-reliance to identify, diagnose, and correct internal problems and failures; self-repair to overcome damage; adaptability to function and explore in new and unknown environments; and extreme efficiency to operate with very limited resources. These are typically characteristics of robust biological systems, and they will also be the characteristics of future aerospace systems. Acquisition of such intelligence, adaptability, and computing power go beyond the present capabilities of microelectronic devices.

The current state-of-the-art microelectronics is rapidly approaching its limit in terms of feature size (0.1 microns). Future enhancements will need novel alternatives to microelectronics fabrication and design as we know them today. Nanotechnology will afford a new class of electronics. In addition to possessing the benefits inherent in smaller feature size, nanotechnology will harness the full power of quantum effects that are operable only at nanoscale distances. Hence, not only should we expect a performance enhancement at the quantitative level, due to the higher packing density of nanoscale components, but also the emergence of qualitatively new functionalities associated with harnessing the full power of quantum effects. The hybridization of nanolithography and bioassembly could serve as the basis of an engineering revolution in the fabrication of complex systems.

We are already seeing the potential of nanotechnology through the extensive research into the production and use of carbon nanotubes, nano-phase materials, and molecular electronics. For example, on the basis of computer simulations and available experimental data, some specific forms of carbon nanotubes appear to possess extraordinary properties: Young's modulus over one Tera Pascal (five times that of steel) and tensile strength approaching 100 Giga Pascal (over 100 times the strength of steel). Recent NASA studies indicate that polymer composite materials made from carbon nanotubes could reduce the weight of launch vehicle — as well as aircraft — by half. Similarly, nanometer-scale carbon wires have 10,000 times better current carrying capacity than copper, which makes them particularly useful for performing functions in molecular electronic circuitry that are now performed by semiconductor devices in electronic circuits. Electronic devices constructed from molecules (nanometer-scale wires) will be hundreds of times smaller than their semiconductor-based counterparts.

However, the full potential of nanotechnology for the systems NASA needs is in its association with biology. Nanotechnology will enable us to take the notion of "small but powerful" to its extreme limits, but biology will provide many of the paradigms and processes for doing so. Biology has inherent characteristics that enable us to build the systems we need: selectivity and sensitivity at a scale of a few atoms; ability of single units to massively reproduce with near-zero error rates; capability of self-assembly into highly complex systems; ability to adapt form and function to changing conditions; ability to detect damage and self repair; and ability to communicate among themselves. Biologically inspired sensors will be sensitive to a single photon. Data storage based on DNA will be a trillion times more dense than current media, and supercomputers modeled after the brain will use as little as a billionth of the power of existing designs. Biological concepts and nanotechnology will enable us to create both the "brains and the body" of future systems with the characteristics that we require. Together, nanotechnology, biology, and information technology form a powerful and intimate scientific and technological triad.

Such technologies will enable us to send humans into space for extended durations with greater degrees of safety. While the vehicle they travel in will have much greater capability and display the same self-protective characteristics of spacecraft, nanotechnology will enable new types of human health monitoring systems and healthcare delivery systems. Nanoscale, bio-compatible sensors can be distributed throughout the body to provide detailed information of the health of astronauts at the cellular level. The sensors will have the ability to be queried by

external monitoring systems or be self-stimulated to send a signal, most likely through a chemical messenger. NASA is currently working with the National Cancer Institute (NCI) to conduct research along these specific lines.

Currently, NASA's program is split primarily between the Office of Aerospace Technology (OAT) with a focus on nanotechnology and the newly formed Office of Biological and Physical Research (OBPR) with a focus on basic research in nanoscience related to biomedical applications. Furthermore, the OAT Program integrates nanotechnology development in three areas:

1. materials and structures
2. nanoelectronics and computing
3. sensors and spacecraft components

A summary of the content of these programs follows.

Materials and Structures

A major emphasis for NASA over the next five years will be the production scale-up of carbon nanotubes; the development of carbon nanotube-reinforced polymer matrix composites for structural applications; and the development of analysis, design, and test methods to incorporate these materials into new vehicle concepts and validate their performance and life. NASA also will explore the use of other materials, such as boron nitride, for high-temperature applications and will research the use of crystalline nanotubes to ultimately exploit the full potential of these materials. In the long term, the ability to create biologically inspired materials and structures provides a unique opportunity to produce new classes of self-assembling material systems without the need to machine or process materials. Some unique characteristics anticipated from biomimetics (that is, "mimicking" biology) include multifunctional material systems, hierarchical organization, adaptability, self healing/self-repair, and durability. Thus, by exploiting the characteristics of biological systems, mechanical properties of new materials can be tailored to meet complex, rigorous design requirements and revolutionize aerospace and spacecraft systems.

Nanoelectronics and Computing

Biologically inspired neural nets have been developed in laboratory demonstrations that allow computers to rapidly account for loss of aircraft control elements, understand the resulting aerodynamics, and then teach the pilot or autopilot how to avoid the loss of the vehicle and crew by an innovative use of the remaining aerodynamic control. Such approaches, coupled with the advances in computing power anticipated from nanoelectronics, will revolutionize the way aerospacecraft deal with condition-based maintenance, aborts, and recovery from serious in-flight anomalies. While aircraft do not require electronic devices that can tolerate the space radiation environment, spacecraft exploration for the Space Science and HEDS Enterprises, e.g., vehicles exploring Mars, the outer planets, and their moons, will require such capabilities. NASA mission planners view such capability as enabling them to conduct *in-situ* science (without real-time Earth operators), where huge amounts of data must be processed, converted to useful information, and then sent as knowledge to Earth without the need for large bandwidth communication systems. A longer-term vision incorporates the added

complexity of morphing devices, circuits, and systems whose characteristics and functionalities may be modified in flight. NASA will support work at the underlying device level, in which new device configurations with new functionalities may be created through intra-device switching.

Sensors and Spacecraft Components

NASA's challenge to detect ultra-weak signals from sources at astronomical distances make every photon or particle a precious commodity that must be fully analyzed to retrieve all of the information it carries. Nanostructured sensing elements, in which each absorbed quantum generates low-energy excitations that record and amplify the full range of information, provide an approach to achieve this goal. NASA will also develop field and inertial sensors with many orders of magnitude enhancement in the sensitivity by harnessing quantum effects of photons, electrons, and atoms. A gravity gradiometer based on interference of atom beams is currently under development by NASA with the potential space-based mapping of the interior of the Earth or other astronomical bodies. Miniaturization of entire spacecraft will entail reduction in the size and power required for all system functionalities, not just sensors. Low-power, integrable nano devices are needed for inertial sensing, power generation and management, telemetry and communication, navigation and control, propulsion, and *in situ* mobility, and so forth. Integrated nano-electro-mechanical systems (NEMS) will be the basis for future avionics control systems incorporating transducers, electromagnetic sources, active and passive electronic devices, electromagnetic radiators, electron emitters, and actuators.

Basic Nanoscience

Foremost among the technological challenges of long-duration space flight are the dangers to human health and physiology presented by the space environment. Acute clinical care is essential to the survival of astronauts, who must face potentially life-threatening injuries and illnesses in the isolation of space. Currently, we can provide clinical care and life support for a limited time, but our only existing option in the treatment of serious illness or injury is expeditious stabilization and evacuation to Earth. Effective tertiary clinical care in space will require advanced, accurate diagnostics coupled with autonomous intervention and, when necessary, invasive surgery. This must be accomplished within a complex man-machine interface, in a weightless environment of highly limited available space and resources, and in the context of physiology altered by microgravity and chronic radiation exposure. Biomolecular approaches promise to enable lightweight, convenient, highly focused therapies guided with the assistance of artificial intelligence enhanced by biomolecular computing. Nanoscopic, minimally invasive technology for the early diagnosis and monitoring of disease and targeted intervention will save lives in space and on Earth. Prompt implementation of specifically targeted treatment will insure optimum use and conservation of therapeutic resources, making the necessity for invasive interventions less likely and minimizing possible therapeutic complications.

BIOMEDICINE EYES 2020

John Watson, National Institutes of Health

I will present ideas from my experience with targeted, goal-oriented research programs and traditional investigator-initiated research projects. I strongly endorse both approaches. For NBIC to reach its potential, national science and engineering priorities should be set to complement investigator-initiated research projects. We should consider including in our NBIC thinking "human performance and health" (not just performance alone) to provide the most for our future quality of life.

How many of us know someone who has undergone angioplasty? A vision for ten and twenty years is under consideration: tomorrow's needs, tomorrow's patients, and tomorrow's diverse society. Well, what about today's needs, today's patients, and today's diverse society? It is riskier to talk about targeting a research goal to solve today's problems than to focus on promising basic research for solving as yet undefined problems.

We do not know what causes atherosclerosis. Surgically bypassing atherosclerotic plaques was shown to have clinical benefit. Using a small balloon to push the plaques into a coronary artery wall, thus opening the lumen, was met with lots of skepticism. If we had waited until we knew all the atherosclerosis basic science, millions of patients would not have benefited from angioplasty.

Picking up on Newt Gingrich's comments about providing some constructive unreasonableness to the conversation, let me suggest expanding our thinking to science and engineering, not science alone. Also, one can compliment our executive branch and Congress for setting national priorities. For discussion today, I will use the example of Congress establishing as a national priority use of mechanical systems to treat heart failure.

If NBIC is to blend into the fifth harmonic envisioned by Newt Gingrich, some national priorities are needed to complement unplanned, revolutionary discoveries. For instance, urinary incontinence a major health problem for today's patients. If the nation had a science and engineering capacity focused on urinary incontinence, this very personal problem would be virtually eliminated. As Mr. Gingrich stated, basic research can be associated with a specific goal..

Table A.1 is a list of the greatest engineering achievements of the past century. The primary selection criterion in constructing this list was worldwide impact on quality of life. Electrification was the number one selection, because the field was fully engineered to improve efficiency, to lower cost, and to provide benefit for virtually everyone. You will notice that healthcare technologies is number 16. NBIC technologies could focus on this field in this century and help move it into the top 10, to the enormous benefit of human performance, health, and overall quality of life.

Table A.1. Greatest Engineering Achievements of the Twentieth Century

1. Electrification	11. Highways
2. Automobile	12. Spacecraft
3. Airplane	13. Internet
4. Water Supply	14. Imaging
5. Electronics	15. Household Appliances
6. Radio and TV	16. Health Technologies
7. Agricultural Mechanization	17. Petroleum Technologies
8. Computers	18. Laser and Fiber Optics
9. Telephones	19. Nuclear Technologies
10. Air Conditioning & Refrigeration	20. High-performance Materials

Setting priorities involves national needs, process, and goals. The Congressional legislative process is quite effective for targeting priorities. The human genome is an example of a work in progress. Today I would like to focus on the field of prevention and repair of coronary heart disease (CHD), where the clinical benefits timeline for today's patients is a little clearer. Successfully addressing priorities such as these usually requires a few decades of sustained public (tax payer) support.

Following hearings in the 1960s, Congress identified advanced heart failure as a growing public health concern needing new diagnostic and treatment strategies. It called for NIH to establish the Artificial Heart Program. Following a decade of system component research, the National Heart, Lung, and Blood Institute (NHLBI) initiated the left ventricular assist device (LVAD) program in 1977. Research and development was targeted towards an implantable system with demonstrated two-year reliability that improved patients' heart function and maintained or improved their quality of life. A series of research phases based on interim progress reviews was planned over a 15-year timeline.

A few years earlier, the NHLBI established less invasive imaging of coronary artery disease as a top priority. A similar program was established that produced less invasive, high-resolution ultrasound, MRI, and CAT scanning for evaluating cardiac function and assessing obstructive coronary artery disease. While this was not an intended outcome, these imaging systems virtually eliminated the need for exploratory surgery. The purpose of long timelines for national programs is not to exclude individual or group-initiated research, and both can have tremendous benefit when properly nurtured.

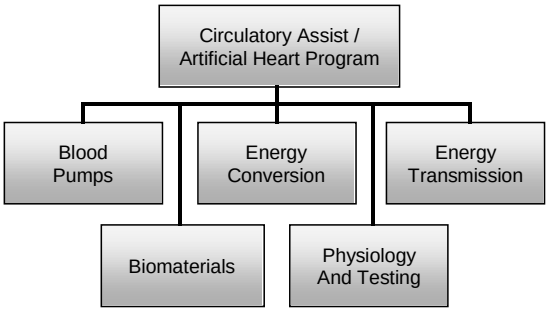

Figure A.4. NHLBI program organization.

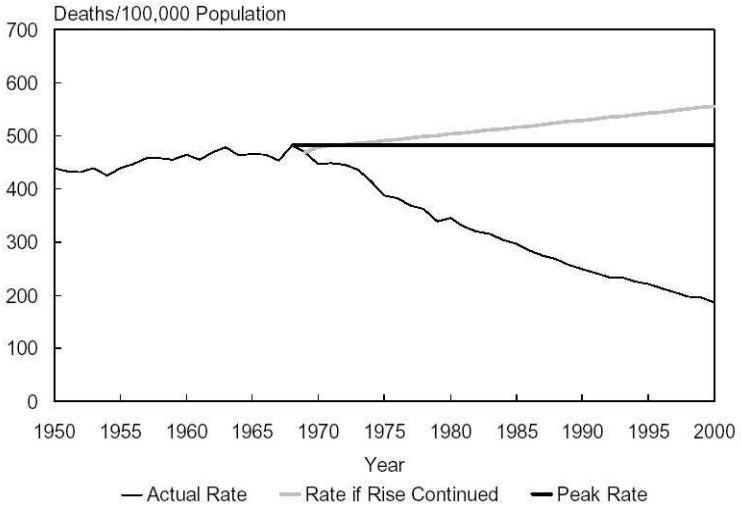

Figure A.6. Coronary heart disease statistics from 1950—1998, age-adjusted to the 2000 standard. CHD accounted for 460,000 deaths in 1998. It would have accounted for 1,144,000 if the rate had remained at its 1963 peak. Comparability ratio applied to rates for 1968-1978.

Heart failure remains a public health issue. At any given time, about 4.7 million Americans have a diagnosed condition of this kind, and 250,000 die each year. The death rates and total deaths from cardiovascular disease have declined for several decades (Fig. A.5). However, during this same time frame, death rates from congestive heart failure (CHF) increased for men and women of all races (Fig. A.6). The most recent interim look at this field estimates that 50,000 to 100,000 patients per year could benefit from left ventricular assist (90 percent of the patients) and

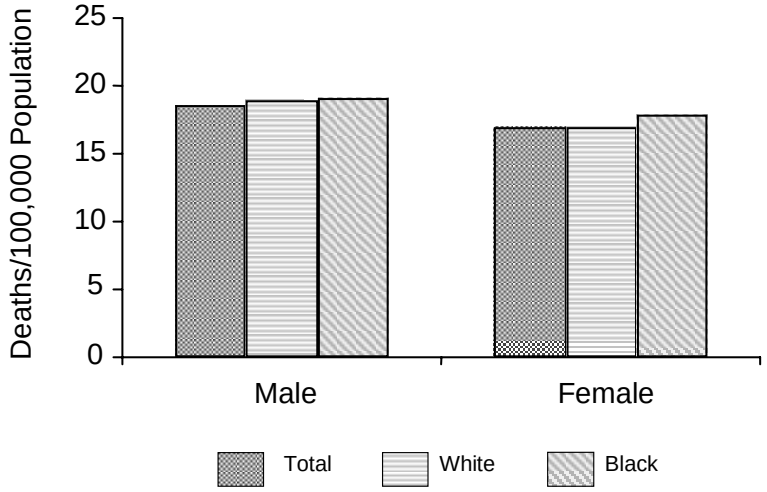

Figure A.5. Age-adjusted death rates for congestive heart failure by race and sex, U.S. 1997. Death rates for CHF are relatively similar in blacks and in whites, but are slightly higher in males than in females.

- **BVS 5000**
- **4,250 patients**
- **33% Discharged**

Figure A.7. Postcardiotomy heart dysfunction.

total artificial heart systems (10 percent of the patients), as reported by the Institute of Medicine in *The Artificial Heart* (1991).

The first clinical systems were designed to support, for days or weeks, the blood circulation of patients with dysfunctional hearts following cardiac surgery. This short-term support would enable the hearts of some patients to recover and establish normal function. More than 4,000 patients treated by a product of this program resulted in 33% being discharged to their homes (Fig. A.7). Prior to this experience, only five to ten percent of these patients were discharged.

Clinicians learned that assist devices could "bridge" patients to cardiac transplant. For advanced heart failure and circulatory collapse, implantable ventricular assist devices restore the patient's circulation, allowing patients to leave the intensive care unit and regain strength before undergoing cardiac transplantation. Many patients received support for over one year, some for two or three years, with one patient supported for over four years. Table A.2 lists a tabulation of some 6,000 patients and the assist device used to discharge them to their homes (50 to 70 percent with cardiac transplants). The question remains, will these systems meet the overall program objective of providing destination therapy for heart failure patients?

Table A.2. Bridge-to-Cardiac Transplant

Device	Number of Patients
Heartmate	3000
Novacor	1290
Thoratec	1650
Cardiowest	206
Discharged	50-70%

To answer this question, the Randomized Evaluation of Mechanical Assistance

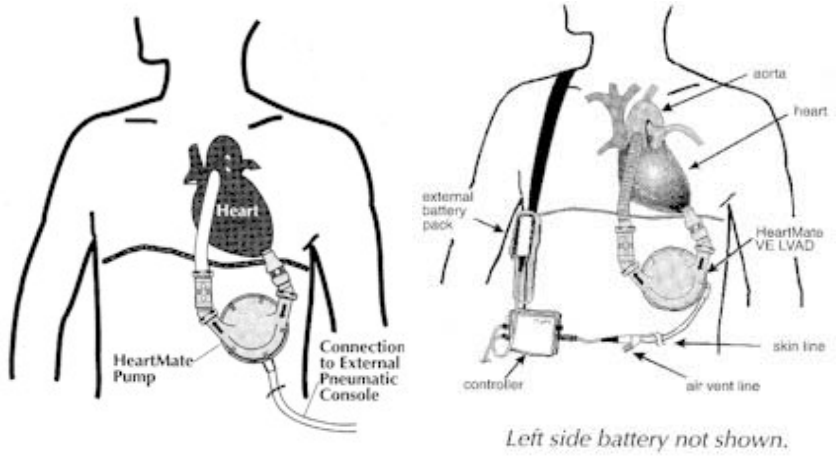

Figure A.8. HeartMate IP and VE.

for the Treatment of Congestive Heart Failure (REMATCH) clinical trial was conducted. The Heartmate left ventricular assist (LVAD) system was used (Fig. A.8). This trial was a true cooperative agreement based on mutual trust among academia, the private sector, and the government. This was a single blind trial, with the company and the principle investigator blinded to the aggregate results of the trial as it was underway. The NHLBI established a Data and Safety Monitoring Board (DSMB) to confidentially review the progress of the trial and evaluate every adverse event. At each meeting, the DSMB recommended to NHLBI if the trial

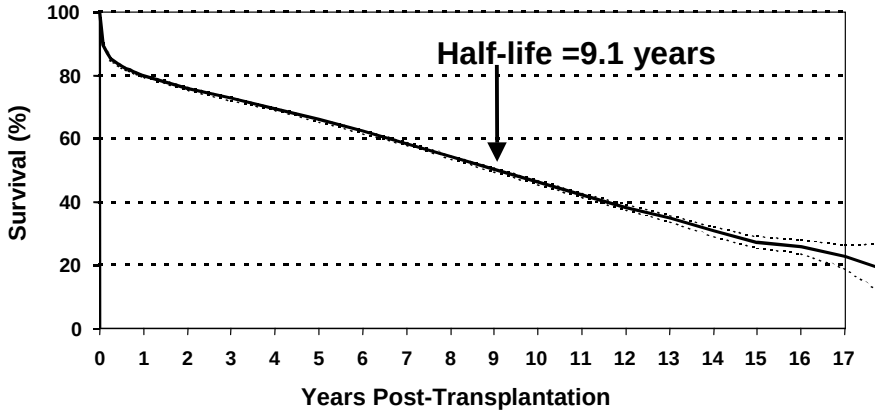

Figure A.9. Heart transplant survival.

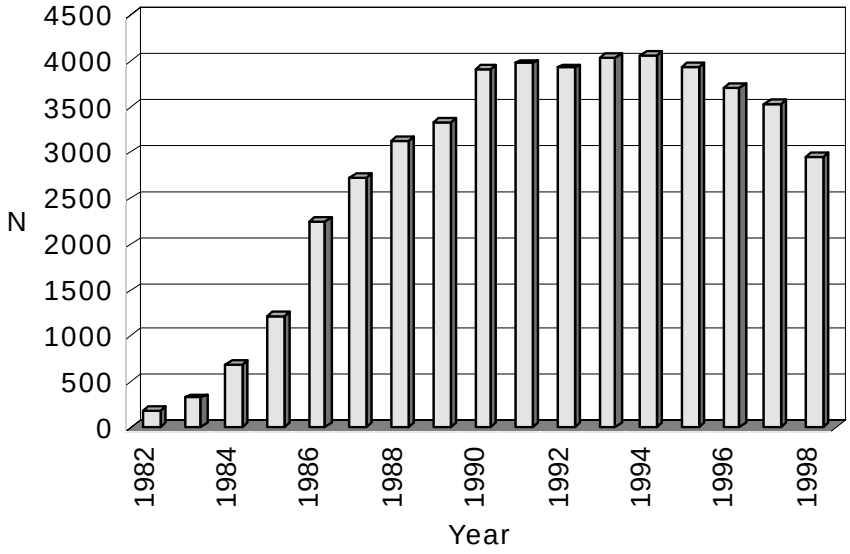

Figure A.10. ISHLT Registry of annualized heart transplant volume.

should continue and what was needed to improve recruitment and the quality of the data. The NHLBI made the final decisions about the conduct of the trial.

It should be noted here that the burden of heart failure on healthcare is increasing. Heart transplants provide remarkable survival and quality of life, but only for some patients, because the limited donor pool provides hearts for only about 2000 patients a year. Figure A.9 is based on a registry of some 52,000 heart transplant patients. The mean survival is nine years, with some patients surviving 15 years or more. These

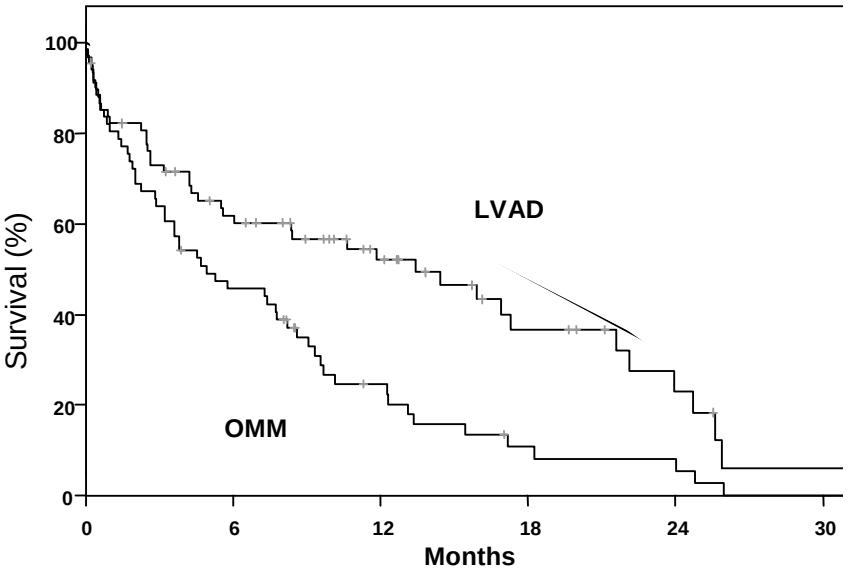

Figure A.11. The LVAD patient improvements in survival.

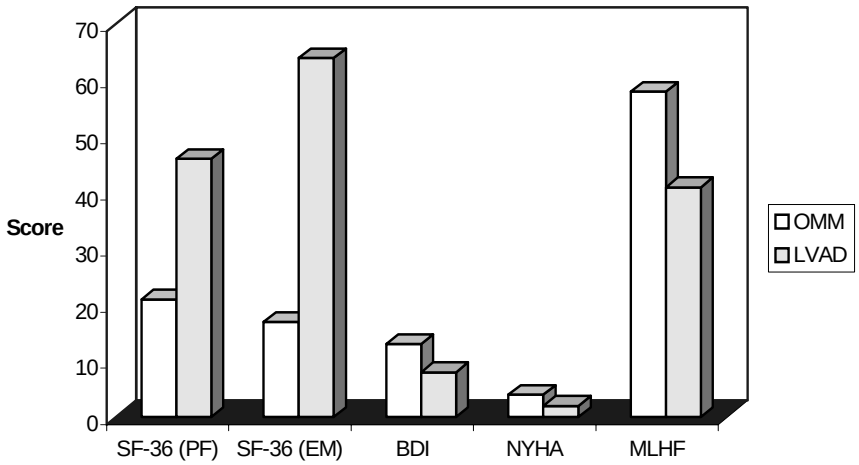

Figure A.12. The LVAD patient improvement in quality of life.

patients serve as the guideline for improved function, quality of life, and survival for alternative therapies (Fig. A.9).

The REMATCH primary end-point was set at a 33 percent improvement in survival for LVAD patients who are not eligible for cardiac transplantation over two years. The goal was for patients to experience improved function without a decrease in quality of life compared to the randomized control group. Cost and cost-effectiveness will also be analyzed as the data becomes available.

The LVAD patients demonstrated a 48 percent improvement in survival (Fig. A.11), significant functional gains, and suggestions of improved quality of life (Fig. A.12), compared with patients receiving optimal medical management (OMM). The LVAD patients also experienced increased adverse events of infections, bleeding, and technical device problems (Table A.3). At two years, updated data (not shown) showed a 200 percent increase in survival but also a high number of device failures.

Table A.3. LVAD Patients' Adverse Events

	Rate per patient-year		
Event	**OMM (n=60)**	**LVAD (n=67)**	**Ratio (95% CI)**
All	2.75	6.45	2.35 (1.86-2.95)
Bleeding (Nonneurological)	0.06	0.56	9.47 (2.3-38.9)
Neurological Dysfunction	0.09	0.39	4.35 (1.31-14.5)
Peripheral Embolic Event	0.06	0.14	2.29 (0.48-10.8)
Sepsis	0.3	0.6	2.03 (0.99-4.13)

Overall, REMATCH patients have a higher mortality than is measured for AIDS or breast, colon, and lung cancer. Based on REMATCH results, LVAD systems will prevent 270 deaths annually per 1000 patients treated — four times as effective as

beta blockers and ace inhibitors, with a quality of life similar to ambulatory heart failure patients (Table A.4). All of the evidence suggests that these factors could improve, with fewer adverse events, following further research and clinical experience.

The potential of LVAD systems is highlighted in the following two examples of patients from the REMATCH trial. The first example is a 35-year-old women. Following her implant, she has married and is enjoying her husband, home, and dogs. The second patient is a 67-year-old man who collapsed on the golf course. He now claims he is playing better golf than ever against those "40-year-old flat bellies."

This program would not have occurred without priority-setting by Congress. The clinical need is still substantial. Without sustained public support, the needed research and development capacity would not have materialized. NBIC holds even greater promise but will not achieve its potential without setting some national long-term research objectives.

Table A.4. REMATCH Results for LVAD Systems

LVAD Mortality Impact	Quality of Life	Adverse Events
LVAD Rx would avert 270 deaths annually per 1000 patients treated	Improved compared to ESHF, yet normalcy not restored	LVAD morbidity still considerable
Nearly 4 times the observed impact of beta-blockers and ACEI (70 deaths prevented per 1000 patients)	Physical function scores similar to hemodialysis and ambulatory heart failure	Infections and mechanical failure obvious targets for device and management improvement
Magnitude of effect commensurate with complexity of intervention	Emotional role scores better than clinical depression and similar to ambulatory heart failure	Rate of neurological events encouraging

BALANCING OPPORTUNITIES AND INVESTMENTS FOR NBIC

R. Stanley Williams and Philip J. Kuekes, Hewlett Packard Labs

Over the course of the last several millennia, human beings have learned that major tasks can be performed much more efficiently by dividing up the workload and sharing it among individuals and groups with specialized skills. Larger and more complex tasks require societies with more capable tools and communications skills. As we view the beginning of the 21st century, the tasks we want to perform have become so complex and the tools we have created so sophisticated, that we are challenged to even describe them coherently. It is time to take a holistic view of how we relate to our technologies and develop strategic approaches to integrating them in a fashion that makes them more adaptable and responsive to human desires and capabilities.

In 2001, we are seeing the simultaneous beginnings of three great technological and industrial revolutions that will spring from advances in fundamental research during the past two decades:

Information Science — the understanding of the physical basis of information and the application of this understanding to most efficiently gather, store, transmit, and process information.

Nanoscale Science — the understanding and control of matter on the nanometer length scale to enable qualitatively new materials, devices, and systems.

Molecular Biology — the understanding of the chemical basis of life and the ability to utilize that chemistry.

The knowledge base in each of these areas has the capacity to increase exponentially for several decades into the future, assuming that the research enterprise is maintained. Each field, by itself, offers tremendous opportunities and potential dangers for society, but the fact that there are three simultaneous technology revolutions is literally unprecedented in human history.

The greatest prospects and challenges will occur in the overlap areas that combine two or all three of the new technologies. The great difficulties are that (1) each area by itself is so large and intricate that no single human being can be an expert in all of it, and (2) that each area has developed a language and culture that is distinct and nearly incomprehensible to those working in the other areas. Thus, we find that the most significant problems are often not those related to any particular technology but are based on the basic inadequacies of human understanding and communication. This all-important human factor requires that we better understand and apply cognition. *Cognitive science* will become an increasingly important field for research and utilization in order to more effectively employ the technologies springing from information, nanoscience, and molecular biology. In turn, these technologies will enable major advances in the study and applications of cognition by allowing the construction and emulation of physical models of brain function.

A concrete example can help to illustrate the potential of these overlapping technologies. Since 1960, the efficiency of computing has increased approximately two orders of magnitude every decade. However, this fact has rarely been factored into solving a grand challenge by trading off computation for other types of work as an effort proceeded. This is largely because humans are used to maintaining a particular division of labor for at least a human generation. When paradigms change at a rate that is faster, humans have a difficult time adjusting to the situation. Thus, instead of a smooth adoption of technological improvements, there are often revolutionary changes in problem-solving techniques. When the human genome project began, the shotgun approach for gene sequencing was not employed, because the speed of computing was too slow and the cost was too high to make it a viable technique at that time. After a decade of steady progress utilizing, primarily, chemical analysis, advances in computation made it possible to sequence the genome in under two years utilizing a very different procedure. Thus, the optimum division of labor between chemical analysis and computation changed dramatically during the solution of the problem. In principle, that change could have been exploited to sequence the genome even faster and less expensively if the division of labor had been phased in over the duration of the effort.

As long as technologies progress at an exponential pace for a substantial period of time, those improvements should be factored into the solution of any grand challenge. This will mean that the division of labor will constantly change as the technologies evolve in order to solve problems in the most economical and timely fashion. For computation, the exponential trend of improvement will certainly continue for another ten years, and, depending on the pace of discovery in the nano- and information-sciences, it could continue for another four to five decades. Similar advances will occur in the areas of the storage, transmission, and display of information, as well as in the collection and processing of proteomic and other biological information. The route to the fastest solution to nearly any grand challenge may lie in a periodic (perhaps biannual) multivariate re-optimization of how to allocate the labor of a task among technologies that are changing exponentially during execution of the challenge.

These thrusts in 21st century science are being recognized by those in academia. Some university deans are calling them the "big O's": *nano*, *bio*, and *info*. These are seen as the truly hot areas where many university faculty in the sciences and engineering want to work. In looking further into the future, we believe that *cogno* should join the list of the big O's.

One way in which academe responds to new opportunities is by creating new disciplines at the intersections between the established divisions. Materials science was created early in the last century at the boundary between chemistry and structural engineering and has evolved as a separate and highly rigorous discipline. Computer science was created in the middle of the last century at the boundary of electrical engineering and mathematics. Now we are beginning to see new transdisciplinary groups coming together, such as chemists and computer scientists, to address new problems and opportunities. One of the problems we face at the turn of this century is that as device components in integrated circuits continue to shrink, they are becoming more difficult to control, and the factories required to build them are becoming extraordinarily expensive. The opportunity is that chemists can inexpensively manufacture components, i.e., molecules, very precisely at the nanometer scale and do so at an extremely low cost per component. Therefore, the new discipline of molecular electronics is arising out of the interactions between computer scientists and chemists. However, developing this new field requires the rigor of both disciplines, the ability to communicate successfully between them, and the proper negotiation process that allows them to optimally share the workload of building new computers. Chemists can make relatively simple structures out of molecules, but they necessarily contain some defects, whereas computer scientists require extremely complex networks that operate perfectly. Economic necessity brings these two very different fields together in what is essentially a negotiation process to find the globally optimal solution of building a working computer from nanometer scale objects at a competitive cost.

There are other very interesting examples of different sciences just beginning to leverage each other. In the bio-info arena, Eric Winfree at the California Institute of Technology is using DNA for self-assembly of complex structures by designing base-pair sequences to construct nano-scaffolding. There is also the whole area of the interaction between biology and information science known as bioinformatics. With the discovery and recording of the human genome and other genomes, we

essentially have the machine language of life in front of us. In a sense, this is the instruction set of a big computer program that we do not otherwise understand: we have only the binary code, not the source code. There is a huge amount of work to reverse-engineer this binary code, and we are going to have to rely on computing power to understand what these programs are doing.

Another arena of extreme importance is the bio-nano intersection, since at the fundamental level these both deal with the same size scale. There will be tremendous opportunities to design and build measurement devices that can reach to the scale of molecules and give us a lot more knowledge about biology than we have now. But the reverse is also true. We are going to learn new ways to manipulate matter at the nanoscale from our huge investment in biology. The current goal of molecular electronics is to combine simple physical chemistry with computer design. But biomolecules have incredible functionality based on four billion years of R&D on very interesting nano-structures. The world is going to make a huge investment over the next few years in the biosciences, and we will be able to leverage much of that knowledge in engineering new nanoscale systems.

Work on the relationship between cognition and information goes back the Turing test (i.e., a test that determines if a computer can fool a human being into thinking it is a person during a short conversation) — ideas Turing had even before computers existed. As more powerful computers have become cheaper, we now have cars that talk to us. How will the next generation of people respond when all kinds of devices start talking to them semi-intelligently, and how will society start reacting to the "minds" of such devices? As well as the coming impact of info on cogno, we have already seen the impact of cogno on info. Marvin Minsky, in his *Society of Mind*, looked at the cognitive world and what we know about the brain and used that to work out a new model of computation.

With nanotechnology literally trillions of circuit elements will be interconnected. There is a set of ideas coming out of the cognitive science community involving connectionist computing, which only starts to make sense when you have such a huge number of elements working together. Because of nanotechnology, we will be able to start experimentally investigating these connectionist computing ideas. The other connection of nanotechnology with the cognitive sciences is that we will actually be able to have nonintrusive, noninvasive brain probes of conscious humans. We will be able to understand tremendously more about what is going on physically in the brains of conscious minds. This will be possible because of measuring at the nanoscale, and because quantum measurement capability will provide exquisitely accurate measurements of very subtle events. Over the next couple of decades, our empirical, brain-based understanding in the cognitive sciences is going to increase dramatically because of nanotechnology. The hardest challenge will be the bio-cogno connection. Ultimately, this will allow us to connect biology to what David Chalmers recognizes as the hard problem — the problem of the actual nature of consciousness.

The topic of discussion at this workshop is literally "How do we change the world?" What new can be accomplished by combining nanoscience, bioscience, information science, and cognitive science? Will that allow us to qualitatively change the way we think and do things in the 21st century? In the course of discussions leading up to this workshop, some of us identified nano, bio, and

information sciences as being the key technologies that are already turning into 21st century industrial revolutions. Where do the cognitive sciences fit in? One of the major problems that we have in dealing with technology is that we do not know how we know. There is so much we do not understand about the nature of knowledge and, more importantly, about the nature of communication. Behind innovative technologies and industrial revolutions there is another dimension of human effort. In order to harness the new scientific results, integrate them, and turn them into beneficial technologies, we need to strengthen the cognitive sciences and begin the task of integrating the four big O's.

THE IMPACT OF CONVERGENT TECHNOLOGIES AND THE FUTURE OF BUSINESS AND THE ECONOMY

James Canton, Institute for Global Futures

The convergence of nanotechnology, biotechnology, information technology, and cognitive science, which together are referred to here as "convergent technologies," will play a dominant role in shaping the future economy, society, and industrial infrastructure. According to the Commerce Department, over one third of GDP is contributed by information technology. This data would suggest that with new technology being introduced daily, the share of GDP driven by technology will increase. Emerging technologies, especially convergent technologies discussed here, are the engines of the future economy. The objective of enhancing human performance is vital to the well-being of individuals and to the future economic prosperity of the nation. The convergent technologies model has yet to be fully mapped. The convergence of nano-, bio-, and information technologies and cognitive science is in the embryonic stages of our understanding. We need to examine the factors driving convergent technologies and the possible impacts on

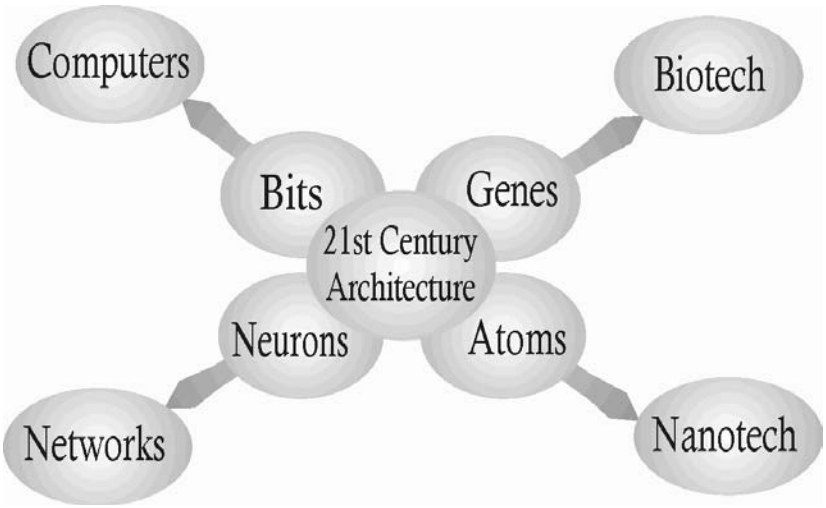

Figure A.13. 21st century architecture.

business and the economy. There is a need to better prepare the nation, coordinate efforts, and work collaboratively towards a national initiative to focus our efforts. How we manage the realtime impact of radical innovation on the social and economic infrastructure of the United States will determine the future wealth, prosperity, and quality of life of the nation. This is no less important than the capacity of the United States to play a global leadership role via the leveraging of next-generation innovations like convergent technologies.

Inventing the Future

Already, massive socio-economic new directions have appeared due to emerging technologies. Examples include the Internet's impact on business, genomics' impact on healthcare, and the wireless impact on personal communications. Some convergence is happening organically, as the evolution of interdisciplinary science, a systems-approach, and the necessity of sharing tools and knowledge is bringing separate disciplines together. The tyranny of reductionism, too long the unwritten law of modern science, is changing, incorporating a more holistic convergent model. We need to take this effort to a new level of fast innovation, inter-science coordination, and action.

The enhancement of human performance via the deployment of convergent technologies requires new work to focus on the synergy of interdependent arenas of science. The benefits to the nation and its citizens may be great in offering lifestyle choices for individuals and incentives for business that do not exist today. New lifestyles, workstyles, and economic business models may be born of this work. The benefits, the payoff we envision, should be the betterment of people and the sustainability of our economy.

It may be possible to influence the ways convergent technologies will change economics and society, on a national scale, by providing leadership and support for a nationwide, collaborative development effort. A national initiative to enhance human performance will be needed. This effort should have many stakeholders in education, healthcare, pharmaceuticals, social science, the military, the economy, and the business sector to name a few. No less than a comprehensive national effort will be required to meet the challenges of a future shaped by convergent technologies.

The daunting challenge of managing rapid and complex technological-driven change is increasingly a disruptive force on today's markets, business, economics, and society. Disruptions will cut more deeply as innovations fostered by convergent technologies emerge more quickly. At the same time, new opportunities will offer unprecedented market leadership for those prepared to exploit them.

Many things will require change: educational curricula, workforce skills, business models, supply chains, and the post-industrial infrastructure, to name a few. Savvy new thinking about the real potential of convergent technology will be required, not just on an individual scale but also relative to the nation's competitive advantages in a global marketplace.

A comprehensive and interdisciplinary strategy needs to be developed that will open up new national policy directions and that can leverage convergent technologies and support the enhancement of human performance and the quality of human life. The future wealth of nations, certainly that of the United States, may

well be based on the national readiness we set in motion today to facilitate the adaptation of our society to the challenges and opportunities of convergent technologies.

Managing Fast Change: The Power Tools of the Next Economy

The exponential progress in technology undeniably influences every aspect of business, the economy, and society. Accelerated change is the daily reality we face — and events are speeding up. These convergent technologies are exponentially increasing in months, not years or decades. Consider that Internet traffic doubles every six months; wireless capacity doubles every nine months; optical capacity doubles every 12 months; storage doubles every 15 months; and chip performance (per Moore's Law) doubles every 18 months.

Will we as a nation be ready to adapt to this pace of change? Will we as a nation be ready to be a global leader in a world where radical technological, social, and economic change occurs overnight, not over a century as in the past? There are vast social policy questions and challenges we have yet to ponder, yet to debate, and yet to understand.

Trying to manage fast and complex change is always a messy business for organizations and people, and even more so for nations. Large systemic change most often happens around a crisis like war or the identification of a potential threat or opportunity. Planned change can backfire. So can policy that attempts to predict the future rather than allow the market economy and free enterprise to rule. Yet there is a role for raising awareness and better directing science policy and private sector coordination that must reflect the changing times.

One would argue that the need to bridge the gap between policy and the fast-changing global market economy may be critically important to the nation's future prosperity and global leadership. A more directed technology policy that is both in sync with the marketplace and capable of rapid responsive change — enabling all sectors of society — would be the preferred direction for the future.

There have been instances where a planned change process was beneficial for the nation such with government management of telecommunications giant ATT as a regulated monopoly. Some innovations are too valuable not to promote in the public's interest. Certainly, supply has driven demand often, such as with the telegraph, train routes, and the telephone. Even the Internet, though never considered by its inventors as the power tool it is today, was built ahead of demand. Enlightened public policymakers understood the immense value of these technologies to shape the economic opportunity of a nation. There are some today who argue with merit for turning the next generation of the Internet, broadband, into a utility so that all Americans can gain access and enhance their productivity.

We are again at a crossroads. The convergence of these critical technologies — nano, bio, info, and cogno — may cause deeper disruptions sooner then any prior technologies. We may not have generations or decades to foster national collaboration. We may have a brief period, perhaps a few years, to raise awareness and committed actions at the national scale before serious global competitive challenges arise.

Convergent Technologies and Human Resources

There already is a crisis of inadequate qualified human resources to manage the future opportunities that may lay before us. Already we confront low math and science test scores in our students. Most of the doctoral students in the technical sciences are from abroad. We have close to one million high-tech jobs a year that go begging. Immigration policy cannot keep pace with attracting the number of skilled knowledge workers our economy needs to grow — and this is only the beginning of the talent wars. Clearly, the emergence of radical innovations in science, such as the convergent technology paradigm described here, will accelerate the nation's need for deep science and technical human resources.

How are we as a nation to compete in the super-charged high-tech global economy of the future if we do not have the skilled human resources? Consider the stakeholders of this crisis and what we must do today to rectify this problem before it becomes the nation's Waterloo. Too long has this message been ignored or simply not addressed with the resources required to make a difference for institutions, the private sector, and individuals.

In our modern era we have seen large transformations in nations due to the globalization of trade, emergence of communications technologies, and the expansion of offshore manufacturing. Increasingly, new technology is emerging as the key driver of change where once the train, the telephone, and before that the steamship, drove economic opportunity.

Given the prospects of advanced NBIC technologies, efforts towards large-systems-managed change represent a daunting task for policymakers across all sectors of society. In some ways, the social policymaking process has lagged behind scientific and technological progress. It is time for the social policymaking process to catch up and reach further to explore the technological vectors that will shape our nation's economic future.

Preparing For the Next Economy

No society has ever had to deal with tools as massively powerful as those that are emerging today. The convergence of the NBIC technologies promise to realign the nation's economic future. These power tools are the key arbiters of the next economy, but they will seem tame compared to what is to come. It could be argued that we have passed over the threshold where it is clear that these power tools will be definitive shapers of nations, economies, and societies. How might we guide the emerging future? How might we invent the preferred future by investing in readiness on a national scale? How might we raise awareness of the radical nature of these technologies so that we can be more productive and focused on enhancing human performance?

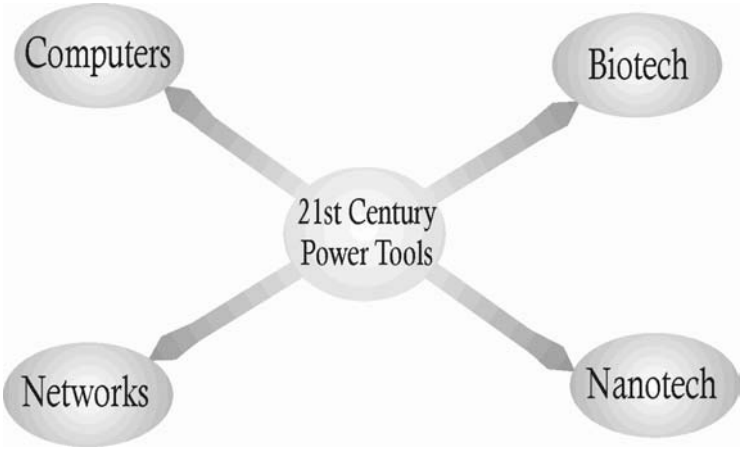

Figure A.14. 21st century power tools.

An entirely new infrastructure is emerging. This new infrastructure will need to accelerate knowledge exchange, networked markets, fast collaborative work, and workforce education. The building blocks of the next economy will be born from the convergent technologies. They represent the shift from the steel and oil of the past and point us towards a radical reshaping of the economy, now in an embryonic stage. The next economy's building blocks — bits, atoms, genes and neurons (Fig. A.15) — will be followed by photons and qubits, as well.

The nations that understand this and that support the growth and development of government and private sector collaboration will thrive. Such collaboration will enable those economies prepared to pursue new economic growth horizons. The future wealth of nations will be based on the change-management readiness we set in motion today by enabling the social adaptation to convergent technology.

How might we direct, encourage, and ultimately shape this desired future for the

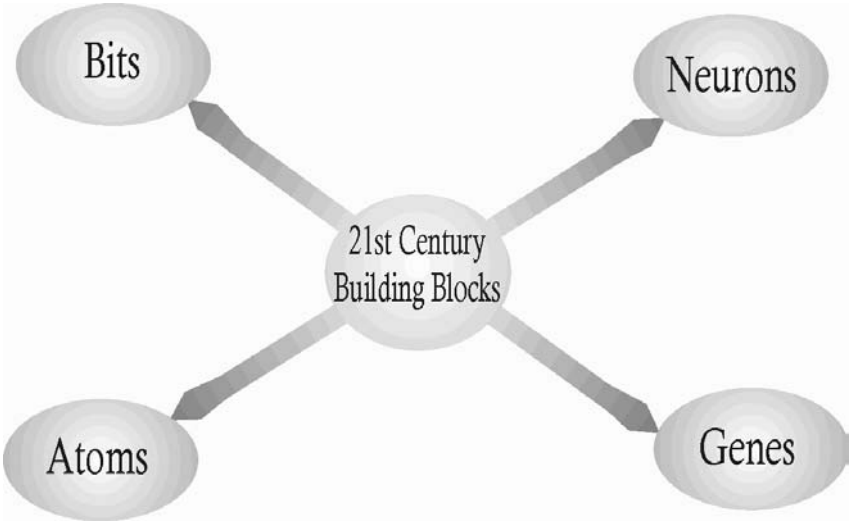

Figure A.15. 21st Century building blocks.

nation, given the emergence of convergent technologies? We can start by developing a plan and setting objectives committed to answering this question. How might we enhance human performance, as a national objective, given the emergence of these convergent technologies? A coordinated and strategic approach will be necessary to create effective long-term results. New thinking will be required that recognizes the necessity of building a collaborative and interdisciplinary strategy for integrating national policy and programs and private and public sector cooperation as never before.

Convergent Technologies: Towards a New Model for Interdisciplinary Policy, Systems-Research, and Inter-Science

Convergent technologies offer an opportunity to design a new model for policyplanners, research scientists, and business executives to consider what the probable outcomes of this work may be. Will we create longevity for the Baby Boomers? Will a new era of convergent knowledge workers be nurtured? How should the private venture community prepare to attract more capital to fuel convergent technology deals? What might healthcare do with enhanced human performance as a medical "product"? What of the ethical and social issues concerning who in our society gets enhanced? These issues and many more are waiting for us in the near future, where convergent technologies will dominate the agenda with breakthroughs too numerous to forecast with any accuracy.

Will we have ready a comprehensive and integrated science policy framework that is visionary enough to consider the development of human potential and the enhancement of human performance? This is the challenge before us, to build a framework that can nurture and experiment but that has the proper controls in place.

The central challenge may well be that we desire a higher quality of life for the nation, as well as building our competitive readiness, given the emergence of convergent technologies. Some may argue against these as non-essential. The quality of life of Americans, it could be easily argued, is influenced heavily by their easy access to leading technologies. American companies and their workers enjoy a global competitive advantage over other less tech-tool-enabled, less human performance-enabled resources. If anything, this may be predictive of the future. We need to continue innovating as a nation and as the leader of the free world. There are security issues not far removed from this argument.

How might we best leverage convergent technology for enhancing the competitive advantage of the nation's businesses and citizens? Nothing less than a comprehensive rethinking of national technology policy, national education policy, and strategic R&D policy should be considered to create the necessary long-term impact that we desire. The U.S. economy is not a planned economy, nor should it be. Yet our nation needs to formulate a new interdisciplinary, inter-science, and systems-wide collaborative model based on converging NBIC technologies in order to move forward to create productive and efficient change. We need to map out the scenarios with all sectors as we stake out our visions of a preferred future.

Convergent Technology Impact Factors

Convergent technologies will be a catalyst for large-systems social change impacting the following domains, all of which will require forward-thinking leadership to facilitate and manage the transition:

1. Workforce Training
2. Educational Curricula
3. Market and Supply Chain Infrastructure
4. Government R&D
5. Private Sector R&D
6. Private Sector Product Development
7. Next Generation Internet

Economic Readiness and Convergent Technology: Key Policy Questions

It could be argued that a nation's technological innovations shape the destiny of that nation. They certainly shape the security, economics, and social well-being of nations. The economic prosperity of the modern nation state cannot be separated from technological adaptation and leadership. But there are other less well-defined issues that we should consider in a global realtime market shaped by convergent technology. Here are some of the arenas yet to be addressed:

1. How can we use the Internet to encourage the high-level knowledge exchange and collaborative work required by convergent technology?
2. What knowledge management resources and large-scale efforts might be mission-essential to facilitate the work with convergent technology?
3. How should private and public sectors work together to facilitate change and adaptation to convergent technology?
4. What new business and economic models might we foster to better enhance productivity in convergent technology?
5. How might we best prepare the nation to compete in a global marketplace shaped by convergent technology?
6. How might we rethink social policy given the future impact of convergent technology?
7. What are the best ways to raise private sector awareness and support for convergent technologies initiatives?
8. Given the emergence of convergent technology, how might we rethink a more holistic inter-science model to better increase our understanding and enhance human performance?
9. How do we define human performance and enhanced human performance given convergent technologies?
10. What is the basis for formulating a national convergent technology initiative to foster private sector and government collaboration, increase citizens' awareness, and coordinate and conduct R&D?

A Proposal for a Convergent Technologies Enterprise Knowledge Network

A convergent technologies Enterprise Knowledge Network (EKN) could provide an online resource bank of information and jobs, a marketplace and clearinghouse for innovations in different vertical industries such as manufacturing, financial services, and entertainment. This network could coordinate information about innovations and intellectual property, and most importantly, connect people using

the power of the Internet. This virtual community would be able to build upon, share, and collaborate on new developments in convergent technologies. This network would be linked to research and the marketplace to be able to quickly disperse information, available capital, breakthroughs, and communications relevant to the convergent technologies community.

Next Steps: Advancing Convergent Technologies to Enhance Human Performance

Convergent technology represents an opportunity to address the need to better share innovations, ideas, knowledge, and perhaps, as is our thesis here, to create more effective breakthroughs in enhancing human performance. This is a process that will have to untangle the silo thinking that has been at the heart of science, government, academia, and research. Given the emerging paradigm of convergent technologies, how might we conceptualize a new systems approach to science?

An adoption of a systems approach is already being explored in many areas: Information technology is considering genetic models; telecommunications is experimenting with self-healing networks; biotechnology is edging towards systems-biology; quantum computing and nanotechology are destined for a convergence.

An area that will require much policy and research work is how we define "enhancing human performance." For the physically-challenged the definition may entail gaining sight or mobility. For the aged, it may entail having access to one's memory. Even bolder, the definition of human enhancement may entail providing people with advanced capabilities of speed, language, skill, or strength beyond what humans can perform today. Just as plastic surgery and pharmacology have given new choices to human beings today, enhancement treatments will no doubt shape tomorrow.

Cybernetic Enhancement

Inevitably, the cybernetic enhancement of human performance is sneaking up on society. We already are "enhanced." We wear contact lens to see better, wear hearing aids to hear better, replace hips to improve mobility. We are already at the point of embedding devices in the heart, brain, and body to regulate behavior and promote health. From braces that straighten teeth to plastic surgery that extends youthful appearance, humans are already on the path towards human performance enhancement. Yet, the next generation of human performance enhancement will seem radical to us today .

Well beyond anticipating the sightless who will see, the lame who will walk, and the infertile couples who will be able to conceive children, we will be faced with radical choices. Who will have access to intelligence-enhancing treatments? Will we desire a genetic modification of our species? The future may hold different definitions of human enhancement that affect culture, intelligence, memory, physical performance, even longevity. Different cultures will define human performance based on their social and political values. It is for our nation to define these values and chart the future of human performance.

Summary

Research into convergent technologies may provide insight into better productivity, enhanced human performance, and opportunities to advance the betterment of individuals. No doubt the business sector will need to be a full player in the strategies to further this approach. Better collaboration within government and between government and the private sector would be a worthwhile endeavor.

The destiny of our nation and the leadership that the United States provides to the world will be influenced by how we deal with convergent technologies and the enhancement of human performance.

Convergent technologies will be a key shaper of the future economy. This will drive GDP higher while the health, prosperity, and quality of life of individuals is improved.

A national initiative that can accelerate convergent technology collaboration and innovation while fostering better inter-agency work and public or private sector work will lead to a prosperous future. Without a strategy that enable collaboration, the development of a true systems approach, and an inter-science model, future success maybe be haphazard. The future destiny of the nation as a global leader may be at risk unless a coordinated strategy is pursued to maximize the opportunity that lies inherent in convergent technologies.

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COHERENCE AND DIVERGENCE OF MEGATRENDS IN SCIENCE AND ENGINEERING

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Scientific discoveries and technological innovations are at the core of human endeavor, and it is expected that their role will increase over time. Such advancements evolve into coherence, with areas of temporary confluence and divergence that bring both synergism and tension for further developments. Six increasingly interconnected megatrends (Fig. A.16) are perceived as dominating the science and engineering (S&E) scene for the next several decades: (a) information and computing, (b) nanoscale science and engineering, (c) biology and bio-environmental approaches, (d) medical sciences and enhancement of human

physical capabilities, (e) cognitive sciences and enhancement of intellectual abilities, and (f) collective behavior and systems approaches.

This paper presents a perspective on the process of identifying, planning, and implementing S&E megatrends, with illustration for the U.S. research initiative on nanoscale science, engineering, and technology. The interplay between coherence and divergence that leads to unifying science and converging technologies does not develop only among simultaneous scientific trends but also over time and across geopolitical boundaries. There is no single way to develop S&E: here is the value of visionary thinking, to anticipate, inspire, and guide development. Scientists with a view of societal implications should be involved from the conceptual phase of any program that responds to an S&E megatrend.

Introduction

Discoveries and advancements in science and technology evolve into coherence reflecting the trends towards unifying knowledge and global society and have areas of both enduring confluence and temporary divergence. The dynamics bring synergism and tension that stimulate further developments following, on average, an exponential growth. Besides addressing societal needs for wealth, health, and peace, a key driver for discoveries is the intrinsic human need for intellectual advancement, to creatively address challenges at the frontiers of knowledge. A few of the most relevant discoveries lead to the birth of megatrends in science and engineering after passing important scientific thresholds, then building up to a critical mass and inducing wide societal implications. After reaching this higher plateau, such discoveries spread into the mainstream of disciplines and are assimilated into general knowledge. S&E megatrends always are traceable to human development and societal needs, which are their origin and purpose (Fig. A.16). We speak about both science and engineering, because engineering skills provide the tools to implement scientific knowledge and thus the capability to transform society.

Funding a megatrend means enhancing the chance to support researchers moving into the respective field while maintaining most of the investment in the original research fields. The goals are to increase the research outcomes of the total investment, obtain the benefits sooner, and create a suitable infrastructure for the new field in the long term.

At times, groups of researchers argue, targeted funding of S&E megatrends could present a threat to open science and technology advancement. We agree that targeted funding may present a threat to the uniform distribution of R&D funding and could present a larger threat to scientific advancement if the megatrend selection were arbitrary. With proper input from the scientific community to identify the megatrend to support, the primary purpose of a focused S&E effort at the national level is the big payoff in terms of accelerated and synergistic S&E development at the frontiers of science and at the interfaces between scientific disciplines. Without such divergent developments, the entire S&E dynamics would be much slower. There is a need for synergy and cooperative efforts among the disciplines supporting a new field of science or engineering, as well as the need to focus on and fund the key contributing disciplines in a timely fashion.

How should society identify an S&E megatrend? A megatrend is usually motivated by a challenge that may appear unfeasible and even unreasonable at the beginning, as were flying, landing on the Moon, or going into the nanoworld. The goals must be sufficiently broad, the benefits sufficiently valuable, and the development time frame sufficiently long to justify national attention and expense. This paper presents an overview of what we see as key national S&E trends in the United States and illustrates the process of identifying a new megatrend in the recent "National Nanotechnology Initiative" (NNI). Finally, the paper discusses the coherence and synergism among major S&E trends and the role of macroscale management decisions.

Six Increasingly Interconnected Megatrends

The S&E communities and society at large share a mutual interest in advancing major new areas of technological focus in response to objective opportunities, with the goal of accelerating the progress of society as a whole. Six increasingly interconnected scientific megatrends, some closely followed by engineering and technology advancements, are expected to dominate the scene for the coming decades in the United States:

1. *Information and computing*. The bit-based language (0,1) has allowed us to expand communication, visualisation, and control beyond our natural intellectual power. Significant developments beginning in the 1950s have not slowed down, and it is expected that we will continue the exponential growth of opportunities in this area. The main product is in the form of software.
2. *Nanoscale science and engineering*. Working at the atomic, molecular, and supramolecular levels allows us to reach directly the building blocks of matter beyond our natural size limitation, that is, on orders of magnitude smaller than what we can see, feel, or smell. At this moment, this is the most exploratory of all megatrends identified in this list. The field was fully recognised in the 1990s and is at the beginning of the development curve. The main outcome of nanotechnology is in the form of hardware, that is, in the creation of new materials, devices, and systems. The nanoscale appears to

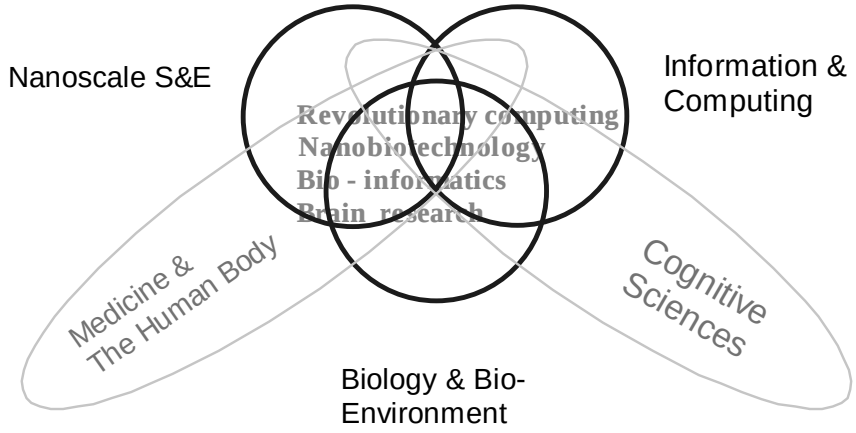

Figure A.16. Coherence and synergism at the confluence of NBIC science and engineering streams.

be the most efficient scale for manufacturing, as we understand its nature now, promising the smallest dissipation of energy, material consumption, and waste and the highest efficiency in attaining desired properties and functions.

3. *Modern biology and bioenvironmental approaches*. Studying cells, their assemblies, and their interactions with their surroundings presents uniquely challenging issues because of their unparalleled complexity. Biology introduces us to self-replicating structures of matter. It uses the investigative methods of information and nanoscale technologies. One important aspect is genetic engineering, another is the connection between life and its environment, including topics such as global warming. Modern biology began its scientific ascendance in the 1970s, and its role continues to expand.
4. *Medical sciences and enhancement of the human body*. The goals are maintaining and improving human physical capabilities. This includes monitoring health, enhancing sensorial and dynamical performance, using implant devices, and extending capabilities by using human-machine interfaces. Healthcare technology is a major area of R&D; it has general public acceptance, and its relative importance is growing as the population ages.
5. *Cognitive sciences and enhancement of intellectual abilities*. This area is concerned with exploring and improving human cognition, behavior, and intellect. Enhancing communication and group interaction are an integral part of improving collective behavior and productivity. This area has received little public recognition, even though increasing cognitive capabilities is a natural objective for a large section of the population.
6. *Collective behavior and systems approach*. This area uses concepts found in architecture, hierarchical systems, chaos theory, and various disciplines to study nature, technology, and society. It may describe a living system, cultural traits, reaction of the society to an unexpected event, or development of global communication, to name a few examples. Recognition of the value of systems approaches increased in the late 1990s.

If one were to model the evolution of the entire society, none of these six S&E megatrends could be disregarded. The nano, bio, and information megatrends extend naturally to engineering and technology, have a strong synergism, and tend to gravitate towards one another. Among these three trends, nanoscale S&E is currently the most exploratory area; however, it is a condition for the development of the other two. Information technology enhances the advancement of both the others. A mathematical formulation of the coherent evolution of research trends could be developed based on a systems approach and time-delayed correlation functions.

Figure A.16. shows a simplified schematic of the complex interaction between the main elements of the scientific system of the beginning of the 21st century. Bits (for computers and communication to satisfy the need for visualization, interaction, and control), genes and cells (for biology and biotechnology), neurons (for cognition development and brain research), and atoms and molecules (to transform materials, devices, and systems) are all interactive components (part of a system approach). But it is important to note that there is a melding of human and S&E development

here: human development, from individual medical and intellectual development to collective cultures and globalization, is a key goal.

The main trends of this 21st century scientific system overlap in many ways; their coherence and synergy at the interfaces create new research fields such as bioinformatics, brain research, and neuromorphic engineering. Let's illustrate a possible path of interactions. Information technology provides insights into and visualization of the nanoworld; in turn, nanotechnology tools help measure and manipulate DNA and proteins; these contribute to uncovering brain physiology and cognition processes; and brain processes provide understanding of the entire system. Finally, the conceived system and architecture are used to design new information technology. *Four transforming tools have emerged: nanotechnology for hardware, biotechnology for dealing with living systems, information technology for communication and control, and cognition-based technologies to enhance human abilities and collective behavior.*

Unifying Science and Engineering

There are several reasons why unifying principles in science and engineering are arising now:

- Scientists have increased their depth of understanding of physical, chemical, and biological phenomena, revealing the fundamental common ground in nature.
- Significant advances exist at the interfaces among disciplines, in such a way that the disciplines are brought closer together and one can more easily identify the common principles, fractal patterns, and transforming tools.
- There is a convergence of principles and methods of investigation in various disciplines at the nanoscale, using the same building blocks of matter in analysis. Now it is possible to explore within human cell and neural systems.
- There is a need to simulate complex, simultaneous phenomena, and hierarchical processes where the known physico-chemico-biological laws are too specific for effective multiscale modeling and simulation. An obvious illustration is the requirements for modeling many-body interactions at the nanoscale, where the laws are specific for each material, and variable within bodies and at the boundaries, at different environmental parameters and for different phenomena.

The unifying science may manifest in three major ways:

- Unification of the basic understanding of various natural phenomena and bringing under the same umbrella various laws, principles, and concepts in physical, chemical, biological, and engineering sciences using cause-and-effect explanation. For example, in physics, there is an increasing awareness that weak, strong, electromagnetic, and gravitational forces may collapse into the same theory in the future (Grand Unified Theory). Mathematical language and other languages for improved communication at S&E interfaces and the system approach offer general tools for this process. Furthermore, unification of knowledge of natural sciences with social sciences and humanities forms *a continuum across levels of increasingly complex architectures and dynamics.*

- Observation of collective behavior in physics, chemistry, biology, engineering, astronomy, and society. *Integrative theories are being developed* using the concepts of self-organized systems, chaos, multi-length and time-scale organizations, and complex systems.
- *Convergence of investigative methods to describe the building blocks of matter at the nanoscale.* The nanoscale is the natural threshold from the discontinuity of atoms and molecules to the continuity of bulk behavior of materials. Averaging approaches specific to each discipline collapse in the same multibody approach.

Identifying and using unifying science and engineering has powerful transforming implications on converging technologies, education, healthcare, and the society in the long term.

National S&E Funding Trends

The foundation of major S&E trends are built up over time at the confluence of other areas of R&D and brought to the front by a catalytic development such as a scientific breakthrough or a societal need. For example, space exploration has grown at the confluence of developments in jet engines, aeronautics, astronomy, and advanced materials and has been accelerated by global competitiveness and defense challenges. Information technology advancement has grown at the confluence of developments in mathematics, manufacturing on a chip, materials sciences, media, and many other areas and has been accelerated by the economic impact of improved computing and communication. Nanotechnology development has its origins in scaling down approaches, in building up from atomic and molecular levels, and in the confluence of better understanding of chemistry, biosystems, materials, simulations, and engineering, among others; it has been accelerated by its promise to change the nature of almost all human-made products. Biotechnology development has grown at the confluence of biology, advanced computing, nanoscale tools, medicine, pharmacy, and others and has been accelerated by its obvious benefits in terms of improved healthcare and new products.

Development of initiatives for such fields of inquiry has led to additional funding for these and similar initiatives. The last two national research initiatives are the Information Technology Research (ITR) initiative, announced in 1999, and the National Nanotechnology Initiative (NNI), announced in 2000. For ITR, there is a report from the President's Information Technology Advisory Committee (PITAC), a committee with significant participation from industry, that shows new elements and expectations. According to this report, the Internet is just a small token development on the way to larger benefits.

How is a new trend recognized for funding? There is no single process for raising an S&E trend to the top of the U.S. national priorities list. One needs to explore the big picture and the long term. It is, of course, important to identify a significant trend correctly; otherwise, either a gold mine may not be exploited, or a wasteful path may be chosen. We note that major U.S. R&D initiatives are designed to receive only a relatively small fraction of the total research budget, because the country must provide support for all fields, including the seeds for future major trends. Generally, one must show a long-term, cross-cutting, high-risk/high-return R&D opportunity in order to justify funding a trend. However, this may be

insufficient. Of the six major trends listed above, only the first two have led to multiagency national research initiatives, although there is *de facto* national priority on the fourth trend — that related to human health. Information technology and nanotechnology received national recognition through the National Science and Technology Council (NSTC). In another example, the driving force for support for a program for global change has been international participation.

Table A.5 summarizes the main reasons for national recognition and funding of several S&E programs. A few years ago, NSF proposed a research focus on biocomplexity in the environment, a beautiful (and actual) subject. This topic so far has not received attention from other funding agencies; a reason may be that no dramatic scientific breakthrough or surge of societal interest was evident at the date of proposal to justify reallocating funds at the national level. On the other hand, cognitive sciences are key for human development and improvement, and it is expected that this area will receive increased attention. Converging technologies starting from the nanoscale is another area for future consideration.

We could relate the S&E developments to the perception and intellectual ability of the contributing researchers. The left-brain handles the basic concepts; the right-brain looks into pictures and assemblies. “Your left-brain is your verbal and rational brain; it thinks serially and reduces its thoughts to numbers, letters, and words. Your

Table A.5. Reasons for national recognition for funding purposes: No unique process of identification of U.S. national R&D programs

(PITAC: Presidential Information Technology Advisory Committee; NSTC: National Science and Technology Council)

S&E Funding Trends in U.S.	Main reasons for recognition at the national level
Information Technology Research (1999 -)	Economic implications; proposed by PITAC; promise of societal implications; recognized by NSTC
National Nanotechnology Initiative (2000 -)	Intellectual drive towards the nanoscale; promise of societal implications; recognized by NSTC
Medicine (NIH)	Public interest in health, and aging population; focus at the National Institutes of Health
Biology and bioenvironment	Distributed interest; NSF focus on biocomplexity
Cognitive	Not yet well recognized; included in education
Collective behavior	Not yet well recognized; not focused, part of others
Others in the last 50 years:	
Nuclear program	National security
Space exploration	International challenge
Global change research	International agreements
Partnerships for a new generation of vehicles	Economic competitiveness; environment

right brain is your non-verbal and intuitive brain; it thinks in patterns, or pictures, composed of "whole things" (Bergland 1985). Accordingly, the brain combines reductionist elements with assembling views into a cooperative and synergistic thinking approach. Those two representations of thinking may be identified as development steps for each S&E megatrend, as illustrated in Table A.6.

It is relevant to keep track of this connection when developing a new research program. For example, the basic concepts originating in the left brain allow individuals and groups to develop representations further from their primary perception (point of reference). Let's consider the human representation of length scale. Initially, we used our hands to measure and developed representations at our natural length scale; then we used mechanical systems, and our representation moved towards the smaller scale of exact dimensions; later, optical tools helped us move into the microscale range of length representation; and electron microscopes and surface probes have helped us move into the nanoscale range. This process continues into the arena of nuclear physics and further on. In a similar manner, abstract concepts handled by the left brain have helped humans move into larger representation scales, beginning with the representation of a building and geography of a territory; later moving to representation of the Earth (useful in sustainable development and global change R&D), then of the universe (needed in space exploration).

The left brain tends to favor reductionist analysis and depth in a single field, which may contribute to "divergent" advancements. Within finite time intervals, such advancements tend to develop faster, to diverge, to take on a life of their own. Meantime, the "whole think" approach is favored by right-brain activities. It is the role of the right brain to assemble the global vision for each initiative and see the coherence among initiatives. This coherence leads to unifying concepts and converging technologies.

Societal feedback is the essential and ultimate test for the nation to establish and assimilate S&E megatrends. There are clear imperatives: increasing wealth, improving healthcare, protecting a sustainable environment, enhancing the culture, and providing national security. When one looks from the national point of view and in the long term, scientific communities, government, and society at large all have the same goals, even if the R&D funds for a megatrend favor some S&E communities in short-term.

Table A.6. S&E megatrends as related to human representation

Left-brain focus	Right-brain focus	S&E trend
DNA, cell (from natural environment)	Biosystems, organisms	Modern biology
Atom, molecule (from natural environment)	Patterns, assemblies	Nanoscale S&E
Bits (chosen language)	Visualization, networking	Information and computing

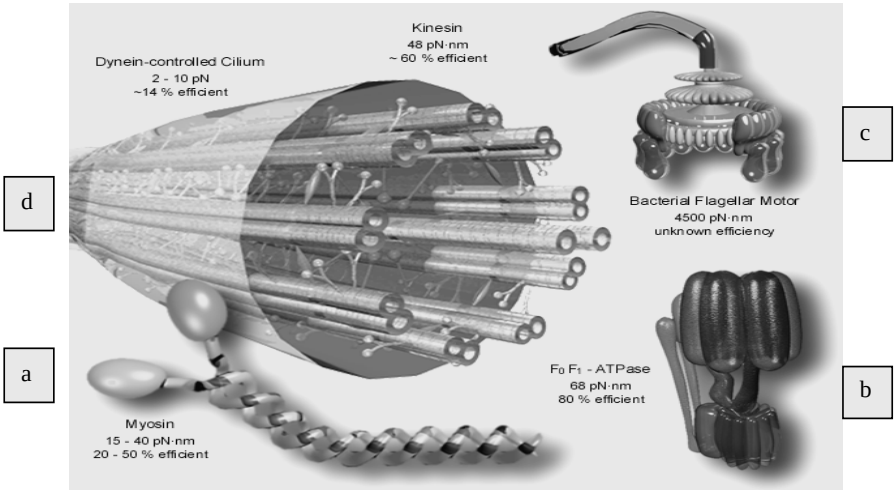

Figure A.17. All living systems work at the nanoscale: illustration of cellular nanomachines (after Montemagno 2001): (a) Myosin, the principle molecular motor responsible for muscle movement (characteristic dimension L about a few nm); (b) ATP synthase, a chemical assembler (L about 10 nm); (c) Bacterial flagella motor (L about 20 nm); (d) A dynein-microtube complex assembled to form a cilium (L about 50 nm).

Motivation, Preparation, and Approval Process of the National Nanotechnology Initiative

Four imperatives define the National Nanotechnology Initiative:

1. There is a need for long-term fundamental research leading to systematic methods of control of matter at the nanoscale. All living systems and man-made products work at this scale. This is because all basic building blocks of matter are established and their basic properties are defined in the range between one and 100 molecular diameters. The first level of organization in biosystems is in the same nanometer range. For example, our body cells typically include nanobiomotors converting energies to the forms needed, such as chemical, electrical, or mechanical. The typical size of the organelles (see Fig. A.17) in a cell is 10 nanometers, which corresponds approximately to 10 shoulder-to-shoulder molecules of water. Fundamental understanding of matter at the nanoscale may change our long-term strategies concerning healthcare, the way we manage the environment, our manufacturing practices. This is the first initiative at the national level motivated by and focused on fundamental research.
2. *Nanotechnology promises to become the most efficient length scale for manufacturing.* While we know that the weak interactions at the nanoscale would require small amounts of energy for manufacturing and that precise assembly of matter would lead to products with high performance and no waste, we do not yet have systematic, economic manufacturing methods for production at the nanoscale. Again, a focus on fundamental research is essential in this regard.

3. *Large societal pay-offs are expected in the long term in almost all major areas of the economy* (see Roco and Bainbridge 2001). Material properties and system functions are adjustable at the nanoscale, a function of size, shape, and pattern. For this reason, nanoscale sciences have created tremendous scientific interest. However, this alone would have not been sufficient to start a national research initiative. Nanotechnology has acquired national interest only in the last two years because of our increasing ability to manufacture products with structures in the nanometer range, as well as to change life and environmental ventures. This possibility promises a new industrial revolution leading to a high return on investments and to large benefits for society.
4. Nanoscience and nanotechnology development are necessary contributing components in the converging advancements in S&E, including those originating in the digital revolution, modern biology, human medical and cognitive sciences, and collective behavior theory. The creation of "hardware" through control at the nanoscale is a necessary square in the mosaic. The future will be determined by the synergy of all six research areas, although in the short term, the synergy will rely on the information, nano- and bio- sciences starting from the molecular length scale. The developments as a result of the convergent technologies will be significant, but are difficult to predict because of discontinuities.

NNI was the result of systematic preparation. It was done with a similar rigor as used for a research project, and documents were prepared with the same rigor as for a journal article. In 1996-1998, there was an intellectual drive within various science and engineering communities to reach a consensus with regard to a broad definition of nanotechnology. In the interval 1997-2000, we prepared detailed materials answering several defining questions:

- What are the research directions in the next 10 years? (See *Nanotechnology research directions. A vision for nanotechnology research and development in the next decade*. Roco, Williams, and Alivisatos 1999/2000; http://nano.gov/nsetrpts.htm.)
- What is the national and international situation? (See *Nanostructure science and technology, A worldwide study*. Siegel et al. 1999; http://nano.gov/ nsetrpts.htm.)
- What are the societal implications? (See *Societal implications of nanoscience and nanotechnology*. NSF 2000; http://nano.gov/nsetrpts.htm.)
- What are the vision and implementation plans for the government agencies? (See NNI, Budget request submitted by the president to Congress. NSTC 2000; http://nano.gov.)
- How do we inform and educate the public at large about nanotechnology? (See *Nanotechnology. Reshaping the world atom by atom*, NSTC/CT 1999; http://nano.gov/nsetrpts.htm.)

The approval process began with various S&E communities, and advanced with the positive recommendations of the Presidential Council of Science Advisory and Technology and of the Office of Management and Budget. The president proposed

NNI on January 21, 2000, in a speech at the California Institute of Technology. The proposed budget was then approved by eight congressional committees, including those for basic science, defense, space, and health-related issues. Finally, the Congress appropriated $422 million for NNI in fiscal year 2001 (see Roco 2001a).

The Role of Macroscale Management Decisions

It is essential that we take time to explore the broad S&E and societal issues and that we look and plan ahead. These activities require information at the national level, including macroscale management decisions, which must be sufficiently flexible to allow creativity and imagination to manifest themselves during implementation of planning and programs. (Firm predictions are difficult because of the discontinuities in development and synergistic interactions in a large system.) Industry provides examples of the value of applying visionary ideas at the macroscale and making corresponding management decisions. At General Electric, for example, Jack Welsh both articulated a clear vision and spearheaded measures structured at the level of the whole company for ensuring long-term success. R&D activities depend on the decisions taken at the macroscale (national), S&E community (providers and users), organization (agency), and individual levels. In addition, the international situation increasingly affects results in any individual country. An international strategy would require a new set of assumptions as compared to the national ones (Roco 2001b).

a) **Strategic macroscale decisions taken at the national level.** These have broad, long-term implications. Different visions and implementation plans may lead to significantly different results. Examples and principles follow.
   - NSF collects information on the evolution of sources of R&D funding like the one shown in Fig. A.18. Federal funding is relatively constant

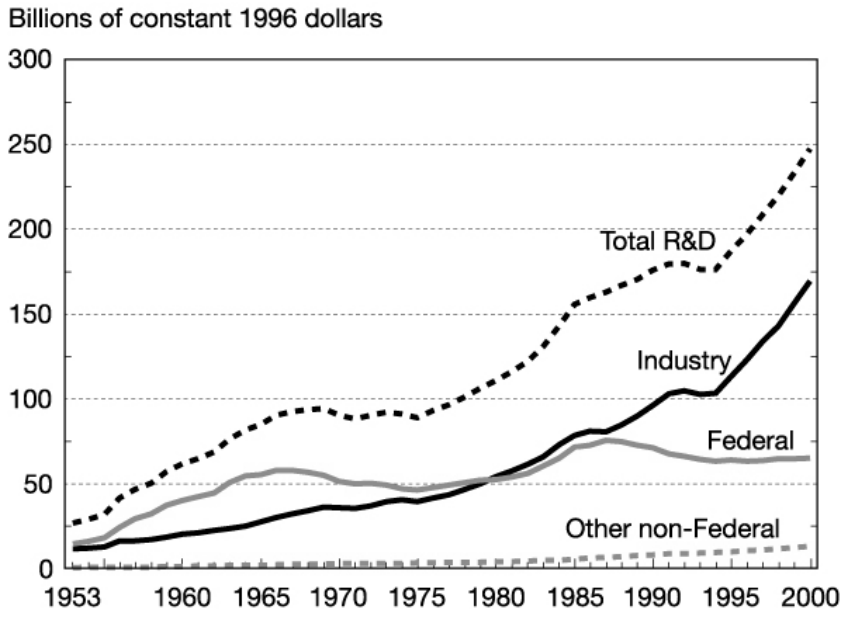

Figure A.18. National R&D funding by source (NSF 2002)

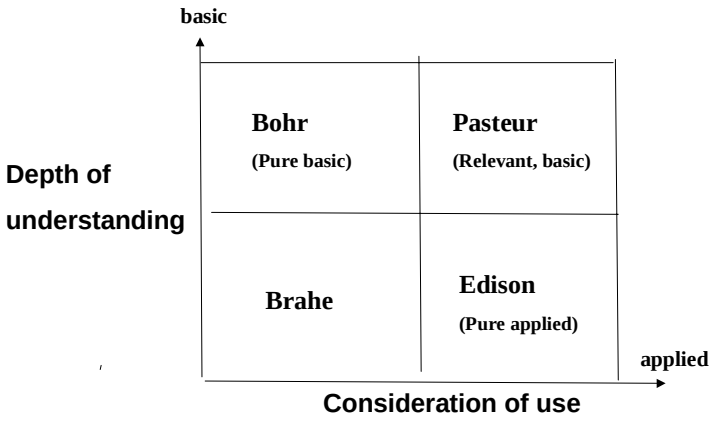

Figure A.19. Pasteur's Quadrant (schematic after Stokes 1997): Redirecting R&D investments with a new role for engineering.

from 1992 to 2000. In the same time interval, private R&D funding has increased and approximately doubled as compared to federal funding. The federal government share of support for the nation's R&D decreased from 44.9 percent in fiscal year 1988 to 26.7 percent in fiscal year 1999. Also, more funds in industry are dedicated to funding development and applied research. That is, society spends more overall for shorter-term outcomes and less for long-term outcomes. Government needs to direct its funding more on complementary aspects: fundamental research (see Bohr's quadrant, Fig. A.19) and mission-oriented projects that encourage depth of understanding, synergism, and collaboration among fields (see Pasteur's quadrant, Fig. A.19). Frequently, the focus in this last quadrant is on developing a generic technology.

- The Federal Government provides funds for industry only under limited programs such as SBIR (Small Business Innovative Research), STTR (Small Technology Transfer), and ATP (Advanced Technology Program at the National Institute of Standards and Technology), or for special purposes such as DARPA (Defense Advanced Research Program Agency). If total funding is constant, supporting applied research often means that a large number of exploratory research projects cannot be funded.
- Since 1970, the proportion of life sciences in the U.S. federal research funding portfolio has increased by about 13 percent, while the engineering sciences have decreased by the same. Relative funding for physical and chemical sciences has decreased, too. This has changed not only the research outcomes, but also the education contents and the overall infrastructure. One way to address this imbalance is to prepare national programs in complementary areas.

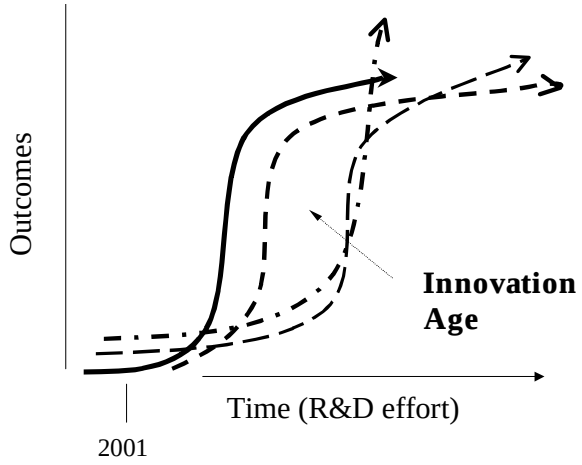

Figure A.20. The "Innovation Age." Organizations will change the focus from repetitive to creative, innovation-based activities and transfer efforts from machines to human development.

- The measures need a collective discipline and flexibility in implementation. A bio-inspired funding approach within the major NNI research areas has been adopted. The funding agencies have issued solicitations for proposals addressing relatively broad R&D themes identified by panels of experts according to the agency missions. In their proposals, researchers respond to those solicitations with specific ideas in a manner suggesting a bottom-up assembly of projects for each theme.
- The coherence among various S&E areas should be evaluated periodically in order to create conditions for convergence and synergism. Figure A.20 suggests that the major trends identified in this paper will play an increased role, beginning with the synergism of nanoscience, modern biology, information technology, and neuro-cognitive sciences, integrated from the molecular level up, with the purpose of enhancing cognitive, human body, and social performance. This coherence will create an unprecedented transformational role for innovation. Organizations will augment creative, knowledge-based activities, with larger conceptual versus physical work components.
- Macroscale measures should address the increased role of the partnerships between the government-sponsored research providers and industry.
- The measures should encourage international collaboration based on mutual interest. The U.S. investments in the areas of nanoscience and nanotechnology represent about one-third of the global investment made by government organizations worldwide. At NSF, support is made available to investigator-initiated collaborations and through activities sponsored by the Foundation.

- National and cultural traditions will provide the diverse support for a creative society, and their role appears to also provide the continuity and stability necessary for a prosperous society.
- The chief aim of taking visionary and macroscale measures is to create the knowledge base and institutional infrastructure necessary to accelerate the beneficial use of the new knowledge and technology and reduce the potential for harmful consequences. To achieve this, the scientific and technology community must set broad goals; involve all participants, including the public; and creatively envision the future. The implementation plans must include measures for stimulating the convergence and beneficial interaction among the S&E megatrends, including coordinated R&D activities, joint education, and infrastructure development.

b) **Strategic decisions taken at the level of R&D providers and users of an S&E megatrend.** The main goal of the strategy adopted by the National Nanotechnology Initiative is to take full advantage of this new technology by coordinated and timely investment in ideas, people, and tools. A coherent approach has been developed for funding the critical areas of nanoscience and engineering, establishing a balanced and flexible infrastructure, educating and training the necessary workforce, promoting partnerships, and avoiding unnecessary duplication of efforts. Key investment strategies are as follows:

- *Focusing on fundamental research.* This strategy aims to encourage revolutionary discoveries and open a broader net of results as compared to development projects for the same resources.
- *Maintaining a policy of inclusion and partnerships.* This applies to various disciplines, areas of relevance, research providers and users, technology and societal aspects, and international integration.
- *Recognizing the importance of visionary, macroscale management measures.* This includes defining the vision of nanotechnology; establishing the R&D priorities and interagency implementation plans; integrating short-term technological developments into the broader loop of long-term R&D opportunities and societal implications, using peer review for NNI; developing a suitable legal framework; and integrating some international efforts. Work done under NSTC (the White House) has allowed us to effectively address such broader issues.
- *Preparing the nanotechnology workforce*. A main challenge is to educate and train a new generation of skilled workers in the multidisciplinary perspectives necessary for rapid progress in nanotechnology. The concepts at the nanoscale (atomic, molecular, and supramolecular levels) should penetrate the education system in the next decade in a manner similar to that of microscopic approach over the last 40 to 50 years.
- *Addressing the broad goals of humanity.* Nanoscale science and engineering must be designed to lead to better understanding of nature, improved wealth, health, sustainability, and peace. This strategy has

strong roots, and, it is hoped, may bring people and countries together. An integral aspect of broader goals is increasing productivity by applying innovative nanotechnology for commerce (manufacturing, computing and communications, power systems, and energy).

- *Identifying and exploiting coherence with other major S&E trends*. As part of an S&E trend, one may address a scientific and technological "grand challenge" at the national level.

c) **Strategic decisions taken at the organizational level.** The organization level is concerned with optimum outcome in each department, agency, national laboratory, or other organization.

d) **Strategic decisions taken at the level of the individual.** The individual level addresses issues related to education, motivation, productivity, and personal involvement.

Common Ground for the Science Community and Society at Large

a) We envision the bond of humanity driven by an **interconnected virtual brain** of the Earth's communities searching for intellectual comprehension and conquest of nature (Roco 1999). In the 21st century, we estimate that scientific and technological innovation will outperform for the first time the societal output of the physical activities separated by geographical borders. Knowledge and technologies will cross multiple institutional boundaries on an accelerated path before application, in a world dominated by movement of ideas, people, and resources. National and cultural diversity will be a strength for the new creative society. The interplay between information, nano-, bio- and healthcare technologies, together with cognitive sciences and cultural continuity will determine the share of progress and prosperity of national communities, no matter what their size.

b) **Researchers need the big picture of different disciplines.** The current focus on reductionism and synthesis in research will be combined with and partially overtaken by a recognition of various aspects of unity in nature and a better understanding of complexity, crossing streams in technology, and crossing national and cultural borders. The ability to see complex systems at the molecular and atomic level will bring a new renaissance. Leonardo da Vinci, equally brilliant in the art of painting and in mechanical, hydraulic, military, and civil engineering, embodied the quintessence of the original Renaissance. The laboratory investigations that began in the 17th century led researchers to separate, reductionist pathways. Today, all disciplines share a common ability to work at the molecular and nano length scales using information technology and biology concepts. The reductionist divergence of sciences and engineering of old seems to be regrouping and finding a confluence. The collective multiphenomena and multiscale behavior of systems between single atoms and bulk have become the center of attention in order to extract new properties, phenomena, and function — like a new alchemy. For researchers to acquire a "big picture" approach requires depth in each discipline and good communication across disciplines.

c) **Visionary R&D planning pays off**. It is essential to take the time to courageously look into the future. "The best way to predict the future is to create it" according to Alan Kaye of Xerox Park. Technological progress may be accelerated by a wise structuring of science and engineering that helps the main trends (or megatrends) be realized sooner and better. Why do all of this? We cite U.S. Federal Reserve Chairman Allen Greenspan (1999), who credits our nation's "phenomenal" economic performance to technological innovation that has accelerated productivity: "Something special has happened to the American economy in recent years . . . . a remarkable run of economic growth that appears to have its roots in ongoing advances in technology."

We have seen in the last 20 years that industrial productivity has steadily increased. This is the key reason why the U.S. economy is growing, indicating the strong connection between science, engineering, and development. The productivity growth rate increased from 0.8 percent during the Carter administration, to 1.6 percent during the Reagan administration, 1.7 percent during the first Bush administration, and 2.1 percent during the Clinton administration. These increases are attributed to technological innovation. Several case studies show that investment in research at the national level also brought about 20 percent additional benefits in the private sector and 50 percent in social return.

Because there is no single or proven way to successfully develop S&E, the role of visionary R&D planning is to set priorities and provide the infrastructure for major promising projects at the national level. The coherence and synergy of various S&E trends and the rate of implementation and utilization are affected by management decisions at the macroscale. The measures must be based on good understanding of the global societal environment and on long-term trends. Professors do not leave their students to do everything they like in academic research. On the contrary, if a research project goes well, more resources are guided in that direction. This idea should be held true at the national level, where there are additional advantages such as synergistic and strategic effects.

d) **The risk of S&E developments should be evaluated in the general context of potential benefits and pitfalls in the long term.** Significant S&E developments inevitably have both desired and undesired consequences. Dramatic discoveries and innovations may create a tension between societal adoption of revolutionary new technologies in the future and our strong desire for stability and predictability in the present. Important research findings and technological developments may bring undesirable negative aspects. Bill Joy has raised such issues with the public, presenting scenarios that imply that nanoscale science and engineering may bring a new form of life, and that their confluence with biotechnology and the information revolution could even place the human species in danger.

In our opinion, raising this general issue is very important, but several of Joy's scenarios are speculative and contain unproven assumptions (see comments from Smalley 2000) and extrapolations. However, one has to treat these concerns responsibly. For this reason we have done studies and tasked coordinating offices at the national level to track and respond to unexpected

developments, including public health and legal aspects. So far, we all agree that while all possible risks should be considered, the need for economic and technological progress must be counted in the balance. We underscore that the main aim of our national research initiatives is to develop the knowledge base and to create an institutional infrastructure to bring about broader benefits for society in the long term. To this end, it is essential to involve the entire community from the start, including social scientists, to maintain a broad and balanced vision.

e) **Contributions to the broader vision and its goals are essential** at any level of activity, including organizational and individual levels. Researchers and funding agencies need to recognize the broad societal vision and contribute to the respective goals in a useful and transforming manner, at the same time allowing the unusual (divergent) ideas to develop for future discoveries and innovations. The funded megatrends provide temporary drivers that seem to be part of the overall dynamics of faster advancements in S&E. The vision and goals should be inclusive and equally understandable by top researchers, the productive sector, and society at large. In a similar manner, one needs to observe the international trends and respond accordingly. Internationalization with free movement of ideas, people, and resources makes impossible long-term advances in only one country. Cultural and national diversity is an asset for creative, divergent developments in S&E.

   In a system with R&D management structured at several levels as discussed above, the macroscale measures have major implications, even if they are relatively less recognized by an S&T community that tends to be more focused on specific outcomes at the organizational and individual levels and on the distribution of funds. The recognition system centered on individual projects in R&D universities and other research organizations may be part of the reason for the limited recognition of the role of macroscale measures.

f) **Maintaining a balance between continuity and new beginnings (such as funding S&E megatrends) is an important factor for progress at all levels.** Coherence and convergence are driven by both intrinsic scientific development (such as work at the interfaces) and societal needs (such as the focus on healthcare and increased productivity). The divergent tendencies are driven also by both internal stimuli (such as special breakthrough in a scientific and engineering field) and external stimuli (such as political direction). We need to stimulate the convergence and allow for temporary divergence for the optimum societal outcomes, using, for example, the mechanisms of R&D funds allocation and enhancing education based on unity in nature. Such activities need to be related to the individual capabilities, where the left-brain (new beginnings) and right-brain (coherence) have analogous dual roles as the drivers of S&E trends.

g) **The societal importance of innovation is growing**, where innovation is defined as “knowledge applied to tasks that are new and different.” In many ways, science and engineering have begun to affect our lives as essential activities because of innovation that motivates, inspires, and rewards us.

While the ability to work has been a defining human quality and increasing industrial productivity was the motor of the 20th century, we see innovation being the main new engine joining other key humanity drivers in the 21st century. The coherence and divergence of major S&E trends are intrinsic processes that ensure more rapid progress in science and technology, enhancing human performance and improving the quality of life. We envision the S&E trends converging towards an ***"Innovation Age"*** in the first half of the 21st century, where creativity and technological innovation will become core competencies. Current changes are at the beginning of that road. They are triggered by the inroads made in understanding the unity of nature manifested equally at the nanoscale and in broad complex systems, by reaching a critical mass of knowledge in physical and biological sciences and their interfaces and by the increased ability to communicate effectively between scientific and engineering fields.

Acknowledgements

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B. EXPANDING HUMAN COGNITION AND COMMUNICATION

THEME B SUMMARY

Panel: W.S. Bainbridge, R. Burger, J. Canton, R. Golledge, R.E. Horn, P. Kuekes, J. Loomis, C.A. Murray, P. Penz, B.M. Pierce, J. Pollack, W. Robinett, J. Spohrer, S. Turkle, L.T. Wilson

In order to chart the most profitable future directions for societal transformation and corresponding scientific research, five multidisciplinary themes focused on major goals have been identified to fulfill the overall motivating vision of convergence described in the previous pages. The first, "Expanding Human Cognition and Communication," is devoted to technological breakthroughs that have the potential to enhance individuals' mental and interaction abilities. Throughout the twentieth century, a number of purely psychological techniques were offered for strengthening human character and personality, but evaluation research has generally failed to confirm the alleged benefits of these methods (Druckman and Bjork 1992; 1994). Today, there is good reason to believe that a combination of methods, drawing upon varied branches of converging science and technology, would be more effective than attempts that rely upon mental training alone.

The convergence of nanotechnology, biotechnology, information technology, and cognitive science could create new scientific methodologies, engineering paradigms, and industrial products that would enhance human mental and interactive abilities. By uniting these disciplines, science would become ready to succeed in a rapid program to understand the structure and functions of the human mind, The Human Cognome Project. Truly, the mind is the final frontier, and unraveling its mysteries will have tremendous practical benefits. Among the most valuable spin-offs will be a host of devices that enhance human sensory capabilities. We will be able to build a vast variety of humane machines that adapt to and reflect the communication styles, social context, and personal needs of the people who use them. We will literally learn how to learn in new and more effective ways, revolutionizing education across the life span. New tools will greatly enhance creativity, industrial design, and personal productivity. Failure to invest in the necessary multidisciplinary research would delay or even prevent these benefits to the economy, to national security, and to individual well-being.

Rapid recent progress in cognitive science and related fields has brought us to the point where we could achieve several breakthroughs that would be of great value to mankind. However, we will need to make a significant special effort to bring together the often widely dispersed scientific and technical disciplines that must contribute. For example, progress in the cognitive neuroscience of the human brain has been achieved through new research methodologies, based in both biology and information science, such as functional magnetic resonance imagining (fMRI) and infrared sensors. However, we are reaching the resolution limits of current instrumentation, for example, because of concerns about the safety of human research subjects (Food and Drug Administration 1998), so progress will stall quickly unless breakthroughs in NBIC can give us research tools with much greater

resolution, sensitivity, and capacity to analyze data. Many other examples could be cited in which scientific, technological, and economic progress is approaching a barrier that can be surmounted only by a vigorous program of multidisciplinary research.

The panel identified five main areas in which integration of the NBIC sciences can enhance the cognitive and communicative aspects of human performance. Each of these is a challenging field for multidisciplinary research that will lead to many beneficial applications.

1. The Human Cognome Project

It is time to launch a Human Cognome Project, comparable to the successful Human Genome Project, to chart the structure and functions of the human mind. No project would be more fundamental to progress throughout science and engineering or would require a more complete unification of NBIC sciences. Success in the Human Cognome Project would allow human beings to understand themselves far better than before and therefore would enhance performance in all areas of human life.

While the research would include a complete mapping of the connections in the human brain, it would be far more extensive than neuroscience. The archaeological record indicates that anatomically modern humans existed tens of thousands of years before the earliest examples of art, a fact that suggests that the human mind was not merely the result of brain evolution but also required substantial evolution in culture and personality. Central to the Human Cognome Project would be wholly new kinds of rigorous research on the nature of both culture and personality, in addition to fundamental advances in cognitive science.

The results would revolutionize many fields of human endeavor, including education, mental health, communications, and most of the domains of human activity covered by the social and behavioral sciences. Some participants in the human cognition and communication working group were impressed by the long-term potential for uploading aspects of individual personality to computers and robots, thereby expanding the scope of human experience, action, and longevity. But at the very least, greater understanding of the human mind would allow engineers to design technologies that are well suited to human control and able to accomplish desired goals most effectively and efficiently. Success in the Human Cognome Project would greatly facilitate success in the other four areas identified by this working group.

2. Personal Sensory Device Interfaces

Fundamental scientific and engineering work needs to be done to permit development of an array of personal sensory device interfaces to enhance human abilities to perceive and communicate. Human senses are notoriously limited. Whereas we can hear ten octaves of musical tones, we can see only one octave of the colors of light, and our ears have a poor ability to form detailed “images” from sound the way our eyes can with light. Today’s communication technology has revolutionized the ability of people to communicate across large distances, but little has been done to help with small area communication, for example, between individuals in a conference room. These are only two of many areas where NBIC sensor efforts can increase human performance.

Research can develop high bandwidth interfaces between devices and the human nervous system, sensory substitution techniques that transform one type of input (visual, aural, tactile) into another, effective means for storing memory external to the brain, knowledge-based information architectures that facilitate exploration and understanding, and new kinds of sensors that can provide people with valuable data about their social and physical environments. For example, increased awareness of the chemical composition of things in our immediate environment will improve human productivity, health, and security. Artificial agents based in microelectronics, nanotechnology, and bioengineering may endow people with entirely new senses or existing senses operating in new ways, in some cases employing neural interfaces to deliver complex information directly into the human mind.

3. Enriched Community

Enlightened exploitation of discoveries in the NBIC sciences will humanize technology rather than dehumanize society. Robots, intelligent agents, and information systems need to be sensitive to human needs, which is another way of saying that they must to some extent embody human personality. Over the next two decades, as nanotechnology facilitates rapid improvement of microelectronics, personal digital assistants (PDAs) are likely to evolve into smart portals to a whole world of information sources, acting as context aware personal brokers interacting with other systems maintained by corporations, governments, educational institutions, and individuals. Today's email and conference call systems could evolve into multi-media telepresence communication environments. Global Positioning System (GPS) units could become comprehensive guides to the individual's surroundings, telling the person his or her location and also locating everything of interest in the immediate locale.

To accomplish these practical human goals, we must invest in fundamental research on how to translate human needs, feelings, beliefs, attitudes, and values into forms that can guide the myriad devices and embedded systems that will be our artificial servants of the future. We must understand how interacting with and through machines will affect our own sense of personhood as we create ever more personable machines. As they become subtle reflections of ourselves, these technologies will translate information between people who are separated by perspective, interests, and even language. Without the guidance provided by the combined NBIC sciences, technology will fail to achieve its potential for human benefit. Multidisciplinary research to humanize computing and communications technology will expand the social competence of individuals and increase the practical effectiveness of groups, social networks, and organizations.

4. Learning How to Learn

We need to explore fresh instructional approaches, based in the NBIC sciences, to help us learn how to learn. Such educational tools as interactive multimedia, graphical simulations, and game-like virtual reality will enhance learning not merely from kindergarten through graduate school but also throughout the entire life course in school, in corporations, and at home. The results of past efforts have often been disappointing, because they failed to draw upon a sufficiently broad and deep scientific base. For example, instructional software typically lacked a firm

grounding in the findings of cognitive science about how people actually think and learn (Bransford, Brown, and Cocking 1999).

In the future, everyone will need to learn new skills and fundamental knowledge throughout life, often in fields connected to mathematics, engineering, and the sciences. Thus we will need new kinds of curricula, such as interactive virtual reality simulations run over the Internet that will allow a student anywhere to experience the metabolic processes that take place within a living cell, as if seeing them from a nanoscale perspective. New, dynamic ways to represent mathematical logic could be developed based on a correct understanding of how the human mind processes concepts like quantity and implication, allowing more people to learn mathematics more quickly, thoroughly, and insightfully. The social interaction resulting from multiuser video games can be harnessed as a strong learning motivator, if they are designed for the user's demographic and cultural background and can infuse the learning with mystery, action, and drama. The goal would be to revolutionize science, mathematics, and engineering education through experiences that are emotionally exciting, substantively realistic, and based on accurate cognitive science knowledge about how and why people learn.

5. Enhanced Tools for Creativity

As technology becomes ever more complex, engineering design becomes an increasingly difficult challenge. For example, it is extremely costly to create large software systems, and the major bottlenecks reducing their effectiveness are unreliability and inefficiency. Similar problems beset systems for large-scale organization administration, supply chain management, industrial design, mass media, and government policy making. We can anticipate that future industries in biotechnology and nanotechnology will present unprecedented design challenges.

Investment in research and development of wholly new industrial design methods will pay great dividends. Among these, biologically inspired techniques, such as evolutionary design methods analogous to genetic algorithms, are especially promising. Terascale and petascale computer simulations are excellent approaches for many design problems, but for the foreseeable future the cost of creating a facility to do such work would be prohibitive for universities and most companies. Therefore, a national center should be established for high-end engineering design simulations. This facility could be linked to a network of users and specialized facilities, providing a distributed design environment for advanced research in engineering. Good models for creating the National Center for Engineering Design would be the supercomputer networks established by the National Science Foundation: the National Computational Science Alliance, the National Partnership for Advanced Computational Infrastructure, and the new Terascale Computing System.

At the same time, radically new methods would enhance small-scale design activities by a wide range of individuals and teams in such fields as commercial art, entertainment, architecture, and product innovation. New developments in such areas as visual language, personalized design, designing around defects, and the cognitive science of engineering could be extremely valuable. Breakthroughs in design could become self-reinforcing, as they energize the economic and technical feedback loops that produce rapid scientific and technological progress.

Statements and Visions

Participants in the human cognition and communication panel contributed a number of *statements*, describing the current situation and suggesting strategies for building upon it, as well as transformative *visions* of what could be accomplished in 10 or 20 years through a concentrated effort. The contributions include statements about societal opportunities and challenges, sensory systems, networking architecture, spatial cognition, visual language, and "companion" computers, as well as visions on predicting social behavior, design complexity, enhancing personal area sensing, understanding the brain, stimulating innovation and accelerating technological convergence.

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STATEMENTS

NBICS (NANO-BIO-INFO-COGNO-SOCIO) CONVERGENCE TO IMPROVE HUMAN PERFORMANCE: OPPORTUNITIES AND CHALLENGES

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This paper is an exploration of new opportunities and challenges for improving human performance from the perspective of rapid technological change and convergence. In the past two million years, human performance has primarily been improved in two ways: evolution (physical-cognitive-social changes to people) and technology (human-made artifacts and other changes to the environment). For example, approximately one hundred thousand generations ago, physical-cognitive-social evolution resulted in widespread spoken language communication among our ancestors. About 500 generations ago, early evidence of written language existed. Then the pace of technological progress picked up: 400 generations ago, libraries existed; 40 generations ago, universities appeared; and 24 generations ago, printing of language began to spread. Again, the pace of technological advancements picked up: 16 generations ago, accurate clocks appeared that were suitable for accurate global navigation; five generations ago, telephones were in use; four, radios; three, television; two, computers; and one generation ago, the Internet.

In the next century (or in about five more generations), breakthroughs in nanotechnology (blurring the boundaries between natural and human-made molecular systems), information sciences (leading to more autonomous, intelligent machines), biosciences or life sciences (extending human life with genomics and proteomics), cognitive and neural sciences (creating artificial neural nets and decoding the human cognome), and social sciences (understanding "memes" and harnessing collective IQ) are poised to further pick up the pace of technological progress and perhaps change our species again in as profound a way as the first spoken language learning did some one hundred thousand generations ago. NBICS (nano-bio-info-cogno-socio) technology convergence has the potential to be the driver of great change for humankind. Whether or not this is in fact desirable, reasoned speculation as to how this may come to pass and the threats posed by allowing it to come to pass are increasingly available from futurists. Currently, this technology road of human performance augmentations is at the stage of macroscopic external human-computer interfaces tied into large social networking systems that exist today. Recently, there are the tantalizing first experiments of microscopic internal interfaces to assist the elderly or others with special needs; and then there is the further speculative road, with potentially insurmountable obstacles by today's standards, that leads to the interfaces of the future.

After setting the stage with longer term visions and imaginings, this paper will focus on the nearer term opportunities and challenges afforded by NBICS research and development (R&D) over the next half a generation or so. In conclusion, while futurists may be overestimating the desirability and feasibility of achieving many of their visions, we are probably collectively underestimating the impact of many of the smaller technological steps along the way.

Introduction: Motivations and Goals

At the beginning of the NBIC workshop, the participants were challenged by Newt Gingrich to think outside the box and to ambitiously consider the possible implications of the nano-info-bio-cogno convergence over the coming decades. We were also instructed to consider human dignity as an important issue, which tempered some of the cyborg speculations and other visions of humans with technology implants and augments that might seem unappealing to most people today. Thus, while social norms can shift significantly over several generations, we were primarily concerned with the world of our children and our own old-age years. We were also treated to a number of presentations describing state-of-the-art results in areas such as nanotechnology; learning technology; social acceptance of technology; designer drugs to combat diseases and other degenerative conditions; neurological implants; advanced aircraft designs highlighting smart, polymorphic (shape-shifting) materials; reports on aging, blindness, and other challenges; evolutionary software and robots; the needs of the defense department for the military of the future; augmented reality and virtual reality; and other useful perspectives on the topic of augmenting human performance. While it would be well beyond the scope of this paper to try to summarize all of these perspectives, I have tried to integrate ideas from these presentations into my own thinking about nano-info-bio-cogno convergence. Additionally, my perspective has been shaped by interactions with Doug Engelbart, whose pioneering work in the area of human

augmentation systems stresses the importance of the co-evolution of technological and social systems. Because the social sciences will strongly influence which paths humans will ultimately explore as well as help us understand why, we are really concerned here with nano-bio-info-cogno-socio convergence.

Nano-bio-info-cogno-socio convergence assumes tremendous advances in each of the component science and technology areas:

1. Nanoscience advances in the coming decade will likely set the stage for a new generation of material science, biochemistry, and molecular electronics, as well as of new tools for measuring and manipulating the world at the level of individual atoms and molecules. Nanotechnology advances are poised to give humans the capabilities that bacteria have had for billions of years, the ability to create molecular machines that solve a wide range of problems on a global scale. Ultimately, these advancements will blur the distinction between natural and human-made objects.
2. Bioscience or life sciences will expand the mapping of the human genome to the human proteome, leveraging both to create new drugs and therapies to address a host of maladies of the past and new threats on the horizon.
3. Information science advances will find many applications in the ongoing e-business transformation already underway, as well as pervasive communication and knowledge management tools to empower individuals. More importantly, information science will provide both the interlingua to knit the other technologies together and the raw computational power needed to store and manipulate mountains of new knowledge.
4. Cognitive science and neuroscience will continue to advance our understanding of the human information processing system and the way our brains work.
5. Social science advances (obtained from studies of real systems as well as simulations of complex adaptive systems composed of many interacting individuals) will provide fresh insights into the collective IQ of humans, as well as interspecies collective IQ and the spread of memes. A meme, which is a term coined by the author and zoologist Richard Dawkins, is “a habit, a technique, a twist of feeling, a sense of things, which easily flips from one brain to another.” It is no coincidence that meme rhymes with gene, for one is about replicating ideas (from one brain to another brain) and the other is about replicating molecules (from one cell to another cell).
6. Thus, the central question of this paper is “how might the convergence of nano-bio-info-cogno-socio technologies be accomplished and used to improve human performance” or, in the words of one workshop participant, Sandia National Laboratory scientist Gerry Yonas, to “make us all healthier, wealthier, and wiser”?
7. To gain some traction on this question, a framework, here termed simply the Outside-Inside Framework, is proposed in the next section. This framework makes explicit four of the key ways that new technologies might be used to augment human performance: (a) outside the body (environmental); (b) outside the body (personal); (c) inside the body (temporary); (d) inside the body (permanent). This framework will be shown to be largely about how and where information is encoded and exchanged: (i) info: bits and the digital

environment, (ii) cogno-socio: brains and memes and the social environments, (iii) nano-bio: bacteria and genes and the bioenvironment, (iv) nano-cogno: bulk atoms, designed artifacts, and the physical environments. In conclusion, near-term implications of NBICS technology convergence will be discussed.

The Outside-Inside Framework and Future Imaginings

The Outside-Inside framework consists of four categories of human performance-enhancing technologies:

- Outside the body and environmental
- Outside the body and personal
- Inside the body and temporary
- Inside the body and permanent

In this section, while briefly describing the categories and subcategories, some extremely speculative visions of the future will be discussed to help stretch our imaginations before "coming back to earth" in the last section to discuss more practical and near term possibilities. Readers are encouraged to view this section as a number of imagination challenges and to create their own answers to questions like what new materials, agents, places, mediators, ingestibles, senses, and species might come to be in the next few decades. In the true spirit of brainstorming, anything goes in this section. Also, it is worth noting that while futurists may be overestimating the desirability and feasibility of how quickly, if ever, we can achieve many of their visions, we are probably collectively underestimating the impact of many of the smaller technological steps along the way. Finally, as an example of improving human performance, the task of learning will be considered, focusing on the way existing and imaginary technologies may improve our ability to learn and/or perform more intelligently.

Outside the Body and Environmental.

People perform tasks in a variety of environmental contexts or places, such as homes, offices, farms, factories, hotels, banks, schools, churches, restaurants, amusement parks, cars, submarines, aircraft, space stations, and a host of other environments that have been augmented by what is termed here environmental technologies. From the materials that are used to construct the buildings and artifacts at these locations to the agents (people, domesticated animals) that provide services in these locations to the very nature of the places themselves, environmental technologies account for most of the advances in human performance that have occurred in the past 500 generations of recorded history (most of us overlap and therefore experience only about five generations of perspectives from grandparents to grandchildren). For the task of learning, consider the important roles that the three innovations — paper (material), teachers (agents), and schools (places) — have had on education. NBICS convergence will surely lead to new materials, new agents, and new places.

Outside the body and environmental: Materials. We expect that the progression from rocks, wood, bricks, cloth, ceramics, glass, bronze, iron, cement, paper, steel, rubber, plastic, semiconductors, and so on, will be augmented with new materials, such as smart, chromatically active (change color), polymorphic (change shape)

materials such as those NASA is already experimenting with. For a thought-provoking vision of where new materials could lead, the reader is directed to the currently infeasible but intriguing notion of "utility fog" developed by Rutgers computer science professor J. Storrs Hall in the early 1990s. Smaller than dust, "foglets" are speculative tiny interlocking machines that can run "programs" that make collections of billions of them work together to assume any shape, color, and texture, from flowing, clear water to fancy seat belt body suits that appear only when an accident has occurred. If utility fog were a reality, most artifacts could be made invisible until needed, making them quite portable. There would be no need to carry luggage on trips; one could simply create clothes out of utility fog. Materializing objects out of thin air (or fog), while wildly infeasible today, nevertheless provides an interesting springboard for imagining some of the ultimate human-computer interfaces (such as a second skin covering human bodies, eyes, ears, mouth, nose, and skin) that may someday exist. Perhaps these ultimate interfaces might connect us to telerobotic versions of ourselves assembled out of utility fog in distance places.

There are many reasons to be skeptical about utility fog (the Energy budget, for one), but notions like utility fog help us understand the potential of NBICS. For example, multi-cellular organisms provide a vast library of examples of the ways cells can be interlinked and grouped to produce shapes, textures, and macroscopic mechanical structures. Social insects like ants have been observed to interlink to solve problems in their environments. And while I'm unaware of any types of airborne bacteria that can spontaneously cluster into large groups, I suspect that mechanisms that bacteria and slime molds use for connecting in various arrangements may one day allow us to create new kinds of smart materials. Hopefully the notion of utility fog has served its brainstorming purpose of imagination stretching, and there are a number of related but nearer term investigations underway. For example, U.C.-Berkeley professor and microroboticist Kris Pister's Smart Dust and Micromechanical Flying Insect projects are good examples of the state-of-the-art in building microrobots, and as these microrobots get smaller, they may very well pave the way to many exciting new materials.

Outside the body and environmental: Agents. Interacting with intelligent agents, such as other people and other species (e.g., guide dogs), has clear advantages for augmenting human performance. Some of the most important agents we interact with daily are role-specialized people and businesses (organization as agent). The legal process of incorporating a business or nonprofit organization is essentially equivalent to setting up a fictitious person with specialized rights, responsibilities, and capabilities. The notion of new agents was an active area of discussion among the workshop participants: from the implications of digital personae (assumed identities on-line) to artificial intelligence and robotics, as well as the evolution of new types of organizations. The successful entrepreneur and futurist Ray Kurzweil has a website *kurzweilai.net* (see Top KurzweilAI News of 2001) that explores these and other futures and interestingly includes Kurzweil's alter-ego, Ramona!, that has been interviewed by the press to obtain Kurzweil's views on a variety of subjects. Undoubtedly, as technology evolves, more digital cloning of aspects of human interactions will occur. An army of trusted agents that can interact on our behalf has the potential to be very empowering as well as the potential to be quite difficult to

update and maintain synchrony with the real you. What happens when a learning agent that is an extension of you becomes more knowledgeable about a subject than you? This is the kind of dilemma that many parents and professors have already faced.

Outside the body and environmental: Places. New places create new opportunities for people. The exploration of the physical world (trade connecting ancient civilization, New World, the Wild West, Antarctica, the oceans, the moon, etc.) and the discovery of new places allows new types of human activities and some previously constrained activities to flourish. For example, the New World enhanced the Puritans' abilities to create the kind of communities they wanted for themselves and their children. Moving beyond the physical world, science fiction writer William Gibson first defined the term *cyberspace*. The free thinking artist and futurist Jaron Lanier, who coined the term *virtual reality*, and many other people have worked to transform the science fiction notion of cyberspace into working virtual reality technologies. Undoubtedly, the digital world will be a place of many possibilities and affordances that can enhance human performance on a wide variety of tasks, including both old, constrained activities as well as new activities. The increasing demand for home game machines and combinatorial design tools used by engineers to explore design possibilities is resulting in rapid advances in the state-of-the-art creation of simulated worlds and places. Furthermore, in the context of learning, inventor and researcher Warren Robinett, who was one of the workshop participants, co-created a project that allows learners to "feel" interactions with simulated molecules and other nanostructures via virtual realities with haptic interfaces. In addition, Brandeis University professor Jordan Pollack, who was also one of the workshop participants, described his team's work in the area of combinatorial design for robot evolution, using new places (simulated worlds) to evolve new agents (robots) and then semi-automatically manifest them as real robots in the real world. Also, it is worth noting that in simulated worlds, new materials, such as utility fog, become much easier to implement or, more accurately, at least emulate.

Outside the Body and Personal

The second major category, personal technologies, are technologies that are outside of the body, but unlike environmental technologies are typically carried or worn by a person to be constantly available. Two of the earliest examples of personal technologies were of course clothing and jewelry, which both arose thousands of generations ago. For hunter gatherers as well as cowboys in the American West, weapons were another form of early personal technology. Also included in this category are money, credit cards, eyeglasses, watches, pens, cell phones, handheld game machines, and PDAs (personal digital assistants). For learners, a number of portable computing and communication devices are available, such as leapfrog, which allows students to prepare for quizzes on chapters from their school textbooks, and graphing calculators from Texas Instruments. Recently, a number of wearable biometric devices have also appeared on the market.

Outside the body and personal: Mediators. Mediators are personal technologies that include cellphones; PDAs; and handheld game machines that connect their users to people, information, and organizations and support a wide range of interactions that enhance human performance. WorldBoard is a vision of an information

infrastructure and companion mediator devices for associating information with places. WorldBoard, as originally conceived in my papers in the mid-1990s, can be thought of either as a planetary augmented reality system or a sensory augment that would allow people to perceive information objects associated with locations (e.g., virtual signs and billboards). For example, on a nature walk in a national park a person could use either heads-up display glasses or a cell phone equipped with a display, camera, and GPS (Global Positioning System) to show the names of mountains, trees, and buildings virtually spliced into the scenes displayed on the glasses or cell phone. WorldBoard mediators might be able to provide a pseudo X-ray vision, allowing construction equipment operators to see below the surface to determine the location of underground buried pipes and cables rather than consulting blueprints that might not be available or might be cumbersome to properly orient and align with reality. The slogan of WorldBoard is "putting information in its place" as a first step to contextualizing and making useful the mountains of data being created by the modern day information explosion.

Human-made tools and artifacts are termed mediators, in this paper, because they help externalize knowledge in the environment and mediate the communication of information between people. Two final points are worth making before moving inside the body. First, the author and cognitive scientist Don Norman, in his book *Things that Make Us Smart* provides an excellent, in-depth discussion of the way human-made tools and artifacts augment human performance and intelligence. Furthermore, Norman's website includes a useful article on the seeming inevitability of implants and indeed cyborgs in our future, and why implants will become increasingly accepted over time for a wider and wider range of uses. A second point worth making in the context of mediators is that human performance could be significantly enhanced if people had more will power to achieve the goals that they set for themselves. Willpower enforcers can be achieved in many ways, ranging from the help of other people (e.g., mothers for children) to mediator devices that remove intentionality from the equation and allow multitasking (e.g., FastAbs electric stimulation workout devices).

Inside the Body and Temporary

The third major category, inside the body temporary technologies, includes most medicines (pills) as well as new devices such as the camera that can be swallowed to transmit pictures of a journey through a person's intestines. A number of basic natural human processes seem to align with this category, including inhaling and exhaling air; ingesting food and excreting waste; spreading infections that eventually overcome the body's immune system; as well as altered states of awareness such as sleep, reproduction, pregnancy, and childbirth.

Inside the body and temporary: Ingestibles. Researchers at Lawrence Livermore National Laboratories have used mass spectrometry equipment to help study the way that metabolisms of different people vary in their uptake of certain chemical components in various parts of the body. Eventually, this line of investigation may lead to precisely calibrating the amount of a drug that an individual should take to achieve an optimal benefit from ingesting it. For example, a number of studies show positive effects of mild stimulants, such as coffee, used by subjects who were studying material to be learned, as well as positive effects from being in the appropriate mental and physical states when performing particular tasks. However,

equally clear from the data in these studies are indications that too much or too little of a good thing can result in no enhancement or detrimental side effects instead of enhanced performance.

With the exception of an Air Force 2025 study done by the Air University, I have not yet found a reference (besides jokes, science fiction plots, and graduate school quiz questions), to what I suspect is someone‘s ultimate vision of this ingestible enhancements subcategory, namely a learning pill or knowledge pill. Imagine that some day we are able to decode how different brains store information, and one can simply take a custom designed learning pill before going to sleep at night to induce specific learning dreams, and when morning arrives the person’s wetware will have been conditioned or primed with memories of the new information. Staggeringly improbable, I know.

Nevertheless, what if someone could take a pill before falling asleep at night, and awaken in the morning knowing or being conditioned to more rapidly learn how to play, for example, a game like chess? If learning could be accelerated in this manner, every night before going to bed, people would have a “learning nightcap.” Imagine an industry developing around this new learning pill technology. The process at first might require someone spending the time to actually learn something new, and monitoring and measuring specific neurological changes that occur as a result of the learning experience, and then re-encoding that information in molecular machines custom-designed for an individual to attach himself or herself to locations in the brain and interact with the brain to create dream-like patterns of activation that induce time-released learning. Businesses might then assign learning pills to their employees, schools might assign learning pills to their students, soldiers might take learning pills before being sent out on missions (per the Air Force 2025 study that mentioned a “selective knowledge pill”), and families might all take learning pills before heading out on vacations. However, perhaps like steroids, unanticipated side effects could cause more than the intended changes.

What makes the learning pill scenario seem so far-fetched and improbable? Well, first of all, we do not understand much about the way that specific bits of information are encoded in the brain. For example, what changes in my brain (short-term and then long-term memory) occur when I learn that there is a new kind of oak tree called a Live Oak that does not lose its leaves in the winter? Second, we do not know how to monitor the process of encoding information in the brain. Third, different people probably have idiosyncratic variations in the ways their brains encode information, so that one person’s encoding of an event or skill is probably considerably different from another person’s. So how would the sharing work, even if we did know how it was encoded in one person’s brain? Fourth, how do we design so many different molecular machines, and what is the process of interaction for time-released learning? Fifth, exactly how do the molecular machines attach to the right parts of the brain? And how are they powered? We could go on and on, convincing ourselves that this fantasy is about as improbable as any that could possibly be conceived. Nevertheless, imagination-stretching warmups like these are useful to help identify subproblems that may have nearer term partial solutions with significant impacts of their own.

Inside the Body and Permanent

The fourth major category, inside the body permanent technologies, raises the human dignity flag for many people, as negative images of cyborgs from various science fiction fare leap immediately to mind. The science fact and e-life writer Chris O'Malley recently wrote a short overview of this area. Excerpts follow:

> Largely lost in the effort to downsize our digital hardware is the fact that every step forward brings us closer to an era in which computers will routinely reside within us. Fantasy? Hardly. We already implant electronics into the human body. But today's pacemakers, cochlear implants, and the like will seem crude — not to mention huge — in the coming years. And these few instances of electronic intervention will multiply dramatically… The most pervasive, if least exciting, use of inner-body computing is likely to be for monitoring our vital stats (heart rate, blood pressure, and so on) and communicating the same, wirelessly, to a home healthcare station, physician's office, or hospital. But with its ability to warn of imminent heart attacks or maybe even detect early-stage cancers, onboard monitoring will make up in saved lives what it lacks in sex appeal... More sensational will be the use of internal computers to remedy deficiencies of the senses. Blindness will, it seems reasonable to speculate, be cured through the use of electronic sensors — a technology that's already been developed. So, too, will deafness. Someday, computers may be able to mimic precisely the signal that our muscles send to our brain and vice versa, giving new mobility to paralysis victims. Indeed, tiny computers near or inside our central processing unit, the human brain, could prove a cure for conditions such as Alzheimer's, depression, schizophrenia, and mental retardation... Ethical dilemmas will follow, as always...

Inside the body and permanent: New organs (senses and effectors). This subcategory includes replacement organs, such as cochlear implants, retinal implants, and pacemakers, as well as entirely new senses. People come equipped with at least five basic senses: sight, hearing, touch, taste, and smell. Imagine if we were all blind but had the other four senses. We'd design a world optimized for our sightless species, and probably do quite well. If we asked members of that species to design a new sense, what might they suggest? How would they even begin to describe vision and sight? Perhaps they might describe a new sense in terms of echolocation, like a species of bats, that would provide a realtime multipoint model of space in the brain of the individual that could be reasoned to be capable of preventing tripping on things in hostile environments.

In our own case, because of the information explosion our species has created, I suggest that the most valuable sixth sense for our species would be a sense that would allow us to quickly understand, in one big sensory gulp, vast quantities of written information (or even better, information encoded in other people's neural nets). Author Robert Lucky has estimated that all senses give us only about 50 bits per second of information, in the Shannon sense. A new high bandwidth sense might be called a Giant UpLoad Process or the GULP Sense. Imagine a sixth sense that

would allow us to take a book and gulp it down, so that the information in the book was suddenly part of our wetware, ready for inferencing, reference, etc., with some residual sense of the whole, as part of the sensory gulp experience. Just as some AI programs load ontologies and rules, the GULP sense would allow for rapid knowledge uptake. A GULP sense would have a result not unlike the imaginary learning pill above. What makes the information-gulping sixth sense and the learning pill seem so fantastic has to do in part with how difficult it is for us to transform information encoded in one format for one set of processes into information encoded in another format for a different set of processes — especially when one of those formats is idiosyncratic human encoding of information in our brains. Perhaps the closest analogy today to the complexity of transforming information in one encoding to another is the ongoing transformation of businesses into e-businesses, which requires linking idiosyncratic legacy systems in one company to state-of-the-art information systems in another company.

The process of creating new sensory organs that work in tandem with our own brains is truly in a nascent state, though the cochlear implant and retinal implant directions seem promising. University of Texas researcher Larry Cauller, who was one of the workshop participants, grabbed the bull by the horns and discussed ways to attack the problem of building an artificial brain as well as recent technology improvements in the area of direct neural interfaces. As neural interface chips get smaller, with finer and more numerous pins, and leveraging RF ID tag technology advances, the day is rapidly approaching where these types of implants can be done in a way that does minimal damage to a brain receiving a modern neural interface implant chip. Improved neural interface chips are apparently already paying dividends in deepening the understanding of the so-called mirror neurons that are tied in with the "monkey see, monkey do" behaviors familiar in higher primates. One final point on this somewhat uncomfortable topic, MIT researcher and author Sherry Turkle, who was also a workshop participant, presented a wealth of information on the topic of sociable technologies as well as empirical data concerning people's attitudes about different technologies. While much of the discussion centered on the human acceptance of new agents such as household entertainment robots (e.g., Sony's AIBO dog), there was unanimous agreement among all the participants that as certain NBICS technologies find their way into more universally available products, attitudes will be shaped, positively as well as negatively, and evolve rapidly, often in unexpected ways for unexpected reasons.

Tokyo University's Professor Isao Shimoyama has created a robo-roach or cyborg roach that can be controlled with the same kind of remote that children use to control radio-controlled cars. Neural interfaces to insects are still crude, as can be seen by going to Google and searching for images of "robo-roach." Nevertheless, projecting the miniaturization of devices that will be possible over the next decade, one can imagine tools that will help us understand the behaviors of other species at a fine level of detail. Ultimately, as our ability to rapidly map genes improves, neural interface tools may even be valuable for studying the relationship between genes and behaviors in various species. NBICS convergence will accelerate as the linkages between genes, cellular development, nervous systems, and behavior are mapped.

Inside the body and permanent: New skills (new uses of old sensors and effectors). Senses allow us to extract information from the world, exchange

information between individuals, and encode and remember relevant aspects of the information in our brains (neural networks, wetware). Sometimes physical, cognitive, and social evolution of a species allows an old sense to be used in a new way. Take, for example, verbal language communication or speech. Long before our ancestors could effectively listen to and understand spoken language, they could hear. A lion crashing through the jungle at them registered a sound pattern in their prehuman brains and caused action. However, over time, a set of sound associations with meaning and abstractions, as well as an ability to create sounds, along with increased brain capacity for creating associations with symbols and stringing them together via grammars to create complex spoken languages, occurred. Over time, large groups of people shared and evolved language to include more sounds and more symbolic, abstract representations of things, events, and feelings in their world. An important point about acquiring new skills, such as sounds in a language, is that infants and young children have certain advantages. Evidence indicates that brains come prewired at the neural level for many more possibilities than actually get used, and if those connections are not needed, they go away. Once the connections go away, learning can still occur, but the infant brain advantage is no longer available. Essentially, the infant brain comes prewired to facilitate the development of new uses of old sensors and effectors.

Entrepreneur and author Bob Horn, who was also a participant at the workshop, argues that visual languages have already evolved and can be further evolved — perhaps, dramatically so for certain important categories of complex information, and thus progressing towards the information gulp-like sense alluded to above. In addition, researchers at IBM‘s Knowledge Management Institute and elsewhere offer stories and story languages as a highly evolved, and yet mostly untapped — except for entertainment purposes — way to rapidly convey large volumes of information. For example, when I mention the names of two television shows, The Honeymooners and The Flintstones, many TV-literate Americans in their forties and fifties will understand that these have in fact the same basic story formula, and will immediately draw on a wealth of abstractions and experience to interpret new data in terms of these stories. They may even be reminded of a Honeymooner episode when watching a Flintstone cartoon — this is powerful stuff for conveying information. The generation of television and videogame enthusiasts have a wealth of new cognitive constructs that can be leveraged in the evolution of a new sense for rapid, high volume information communication. Certainly, new notations and languages (e.g., musical notation, programming languages, and mathematics) offer many opportunities for empowering people and enhancing their performance on particular tasks. All these approaches to new uses of old senses are primarily limited by our learning abilities, both individually and collectively. Like the evolution of speech, perhaps new portions of the brain with particular capabilities could accelerate our ability to learn to use old senses in new ways. An ability to assimilate large amounts of information more rapidly could be an important next step in human evolution, potentially as important as the evolution of the first language spoken between our ancestors.

Inside the body and permanent: New genes. If the notion of “computers inside” or cyborgs raise certain ethical dilemmas, then tinkering with our own genetic code is certain to raise eyebrows as well. After all, this is shocking and frightening stuff

to contemplate, especially in light of our inability to fully foresee the consequences of our actions. Nevertheless, for several reasons, including, for the sake of completeness in describing the Outside-Inside Framework, this is an area worth mentioning. While selective breeding of crops, animals, and people (as in ancient Sparta) is many hundreds of generations old, only recently have gene therapies become possible as the inner working of the billion-year-old molecular tools of bacteria for slicing and splicing DNA have been harnessed by the medical and research communities. Just as better understanding of the inner working of memory of rodents and its genetic underpinnings have allowed researchers to boost the IQs of rodents on certain maze running tasks, soon we can expect other researchers building on these results to suggest ways of increasing the IQs of humans.

University of Washington researcher and medical doctor Jeffrey Bonadio (Bonadio 2002), who was a workshop participant, discussed emerging technologies in the area of gene therapies. Gene therapy is the use of recombinant DNA as a biologic substance for therapeutic purposes, using viruses and other means to modify cellular DNA and proteins for a desired purpose.

In sum, the Outside-Inside Framework includes four main categories and a few subcategories for the ways that technology might be used to enhance human performance:

- Outside the body and environmental
  - new materials
  - new agents
  - new places
  - new mediators (tools and artifacts)
- Outside the body, personal
  - new mediators (tools and artifacts)
- Inside the body, temporary
  - new ingestibles
- Inside the body, permanent
  - new organs (new sensors and effectors)
  - new skills (new uses of old sensors and effectors)
  - new genes

The four categories progress from external to internal changes, and span a range of acceptable versus questionable changes. In the next section, we'll consider these categories from the perspective of information encoding and exchange processes in complex dynamic systems.

Information Encoding and Exchange: Towards a Unified Information Theoretic Underpinning

The Outside-Inside Framework provides one way to organize several of the key issues and ideas surrounding the use of NBICS technology advances to enhance human performance ("make us all healthier, wealthier, and wiser"). This simple framework can be shown to be largely about understanding and controlling how,

where, and what information is encoded and exchanged. For example, consider the following four loosely defined systems and the way information is encoded differently, and interdependently, in each: (a) bits and the digital environment (information), (b) brains and memes and the social environment (cogno-socio), (c) bacteria and genes and the bioenvironment (nano-bio), (d) bulk atoms, raw materials, designed artifacts, and the physical environment (nano-based).

At this point, a brief digression is in order to appreciate the scale of successful information encoding and evolution in each of these loosely defined systems. People have existed in one form or another for about 2 million years, which is a few hundred thousand generations (to an order of magnitude). Today, there are about six billion people on Earth. The human body is made up of about 10^{13} cells, the human brain about 10^{10} cells (10^{27} atoms), and the human genome is about 10^{9} base pairs. Humans have been good problem solvers over the generations, creating successful civilizations and businesses as well as creating a growing body of knowledge to draw on to solve increasingly complex and urgent problems. However, in some ways, even more impressive than humans are bacteria, according to author Howard Bloom (2001). Bacteria have existed on Earth for about 3.5 billion years, which is an estimated 10^{14} bacteria generations ago. Today, there are an estimated 10^{30} bacteria (or about one hundred million bacteria for every human cell) on Earth living inside people, insects, soil, deep below the surface of the Earth, in geothermal hot springs in the depths of the ocean, and in nearly every other imaginable place. Bacteria have been successful "problem-solvers," as is evidenced by their diversity and ever-growing bag of genetic tricks for solving new problems. People have made use of bacteria for thousands of generations (though electronic digital computers only recently) in producing bread, wine, and cheese, but only in the past couple of generations have bacteria become both a tool kit and a road map for purposeful gene manipulation. Bacteria and viruses are both an ally and a threat to humans. For example, bacterial or viral plagues like the influenza outbreak of 1917 are still a major threat today. Among our best new allies in this fight are the advances in life sciences technologies enabled by more powerful digital technology. Most recently, electronic transistors have been around for less than a century, and at best, we have only a few dozen generations of manufacturing technology. Today, there are more than 10^{18} transistors on Earth, and very roughly 10 million transistors per microprocessor, 100 million PCs manufactured per year, and 10 billion embedded processors.

Returning to the issue of understanding and controlling how, where, and what information is encoded and exchanged, consider the following milestones in human history (where GA is human generations ago), as seen through the lens of the Outside-Inside Framework:

- Speech (100,000 GA): A new skill (new use of old sensors and effectors, requires learning a new audible language), encoding information in sounds, for exchanging information among people. Probably coincides with the evolution of new brain centers, new organs.
- Writing (500 GA): A new mediator and new skill (new use of old sensors and effectors, requires learning a new visual language), encoding information in visual symbols on materials from the environment for recording, storing, and

exchanging information between people. Did not require new brain centers beyond those required for spoken language.

- Libraries (400 GA): A new place and agent (organization) for collecting, storing and distributing written information.
- Universities (40 GA): A new place and agent (organization) for collecting, storing, and distributing information as social capital.
- Printing (14 GA): A new mediator (tool) for distributing information by making many physical copies of written and pictorial information.
- Accurate clocks (16 GA): A new mediator (tool) for temporal information and spatial information (accurate global navigation).
- Telephone (5 GA): A new mediator (tool) for exchanging audio information encoded electrically and transported via wires over great distances.
- Radio (4 GA): A new mediator (tool) for distributing audio information encoded electromagnetically and transported wirelessly over great distances.
- Television (3 GA): A new mediator (tool) for distributing audiovisual information encoded electromagnetically, transported wirelessly over great distances.
- Computers (2 GA): A new mediator and agent for storing, processing, creating, and manipulating information encodable in a binary language.
- Internet (1 GA): A new mediator for distributing information encodable in a binary language.
- Global Positioning System or GPS (0 GA): A new mediator for spatial and temporal (atomic clock accuracy) information.

Stepping back even further for a moment (per Bloom 2001), we can identify six fundamental systems for encoding and accumulating information: matter, genes, brains, memes, language, and bits:

- Big Bang (12 billion years ago): New place and new material - the Universe and matter
- Earth (4.5 billion years ago): New place and new materials - the Earth and its natural resources
- Bacteria (3.5 billion years ago): New species and agent, encoding information in primitive genome (DNA) in cells
- Multicellular (2.5 billion years ago): New species with multicellular chains and films
- Clams (720 million years ago): New species with multiple internal organs with primitive nervous systems
- Trilobites (500 million years ago): New species with simple brains for storing information (memes possible)
- Bees (220 million years ago): New species and agent; social insect with memes, collective IQ

- Humans and Speech (2 million years ago): New species and agent, with primitive spoken language and tools, extensive memes, collective IQ
- Writing (about 10 thousand years ago): New mediator, recordable natural language and symbolic representations
- Computers (about 50 years ago): New mediator and agent, binary language and predictable improvement curve through miniaturization

Of course, all these dates are very approximate. The important point is simply this: if the past is the best predictor of the future, then we can expect NBICS convergence to shed light on all of these key systems for encoding, exchanging, and evolving information. If (and this is a big if) we can (1) truly understand (from an information processing standpoint) the working of material interactions, genes and proteins, nervous systems and brains, memes and social systems, and natural language, and translate all this into appropriate computational models, and (2) use this deep model-based understanding to control and directly manipulate their inner workings to short-cut the normal processes of evolution, then perhaps we can create improvements (solve complex urgent problems) even faster. Of course, accelerating evolution in this way is both staggeringly difficult to do in reality as well as potentially very empowering and dangerous if we should succeed.

Again, the point here is simply that NBICS convergence has zeroed in on the key, few separate information systems that drive enhancements not only to human performance, but to the universe as we know it: matter, genes, brains, memes, language, and bits. Does this mean that we have bitten off too much? Perhaps, but it does seem to be time to ask these kinds of convergence questions, much as physicists in the late 1800s began a quest to unify the known forces. In essence, the quest for NBICS convergence is looking for the Maxwell's equations or, better yet, the "unified field theory" for complex dynamic systems that evolve, but in terms of models of information encoding, and exchange instead of models of particle and energy exchange. Author and scientist Richard Dawkins in his book *The Selfish Gene* foreshadows some of this thinking with his notion of a computational zoology to better understand why certain animal behaviors and not others make sense from a selfish gene perspective. Author and scientist Stuart Kaufman in his book *At Home in the Universe: The Search for the Laws of Self-Organization and Complexity* is searching for additional mechanisms beyond evolution's natural selection mechanism that could be at work in nature. Testing and applying these theories will ultimately require enormous computational resources.

It is interesting to note that computational power may become the limiting factor to enhancing human performance in many of the scenarios described above. What happens when Moore's Law runs out of steam? To throw one more highly speculative claim into the hopper, perhaps quantum computing will be the answer. Recently, IBM researchers and collaborators controlled a vial of a billion-billion (10^{18}) molecules designed to possess seven nuclear spins. This seven qubit quantum computer correctly factored the number 15 via Shor's algorithm and had its input programmed by radio frequency pulses and output detected by a nuclear magnetic resonance instrument. Certainly, there is no shortage of candidates for the next big thing in the world of more computing power.

Concluding Remarks: Near-Term Opportunities for e-Business Infrastructure

So what are the near-term opportunities? The R&D community is engaged. From an R&D perspective, the five innovation ecosystems (university labs, government labs, corporate labs, venture capital backed start-ups, and nonprofit/nongovernment organizations) have already geared up initiatives in all the separate NBICS (nano-bio-info-cogno-socio) areas, somewhat less in socio, and cogno is perhaps secondary to neuro. However, what about real products and services coming to market and the converged NBICS as opposed to separate threads?

From a business perspective, a number of existing technology trends generally align with and are supportive of NBICS directions. One of the major forces driving the economy these days is the transformation of businesses into e-businesses. The e-business evolution (new agent) is really about leveraging technology to enhance all of the connections that make businesses run: connections to customers, connections to suppliers, connections between employees and the different organizations inside a business, and connections to government agencies, for example. Some aspects of the NBICS convergence can not only make people healthier, wealthier, and wiser, but can make e-businesses healthier, wealthier, and wiser as well. I suspect that while many futurists are describing the big impact of NBICS convergence on augmenting human performance, they are overlooking the potentially larger and nearer term impacts of NBICS convergence on transforming businesses into more complete e-businesses. The area of overlap between what is good for business and what is good for people is in my mind one of the first big, near term areas of opportunity for NBICS convergence. Improving human performance, like improving business performance will increasingly involve new interfaces to new infrastructures.

a) *Communication infrastructure*: The shift from circuits to packets and electronics to photonics and the roll out of broadband and wireless will benefit both businesses and individuals.

b) *Knowledge infrastructure*: Knowledge management, semantic search, and natural language tools will make businesses and people act smarter.

c) *Sensor infrastructure*: Realtime access to vital information about the health of a person or business will be provided.

d) *Simulation infrastructure*: There will be a shift from *in vitro* to *in silico* biology for the design and screening of new drugs for people and new products for businesses.

e) *Intellectual property, valuations and pricing, human capital infrastructure*: Inefficiencies in these areas are a major drag on the economy overall.

f) *Miniaturization, micromanipulation, microsensing infrastructure*: Shrinking scales drive chip businesses and open new medical applications.

g) *Computing infrastructure (grid - social)*: This is still emerging, but ultimately, computer utility grids will be an enormous source of computing power for NBICS efforts.

h) *Computing infrastructure (autonomic - biological)*: The cost of managing complex technology is high; the autonomic borrows ideas from biological systems.

Already, IBM Research has begun to articulate some of the challenges and the promise of autonomic computing (http://www.research.ibm.com/autonomic/), which seeks to build a new generation of self-managing, self-regulating, and self-repairing information technology that has some of the advantages of living systems. As NBICS convergence happens, our information technology infrastructure will benefit, making many businesses more efficient and more viable.

Ultimately, NBIC convergence will lead to complete computational models of materials, genes, brains, and populations and how they evolve, forever improving and adapting to the demands of changing environments. A first step is to understand the way information is encoded and exchanged in each of these complex dynamic systems and to apply that new understanding to enhance each system. While this is an exciting undertaking, especially in light of recent advances in mapping the human genome, nanotechnology advances, and 30 some years of unabated miniaturization (Moore's Law) driving up computational capabilities, it is also a time to admit that this is still a multi-decade undertaking with lots of twists and turns in the road ahead. Better frameworks that help us inventory and organize the possibilities, as well as glimpse the ultimate goal of NBICS convergence, are still needed.

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SENSOR SYSTEM ENGINEERING INSIGHTS ON IMPROVING HUMAN COGNITION AND COMMUNICATION

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The improvement of human cognition and communication can benefit from insights provided by top-down systems engineering used by Raytheon and other aerospace and defense companies to design and develop their products. Systems engineering is fundamental to the successful realization of complex systems such as multifunction radar sensors for high performance aircraft or the Army's Objective Force Warrior concept for the dismounted soldier. Systems engineering is very adept at exploring a wide trade space with many solutions that involve a multitude of technologies. Thus, when challenged by the theme of the workshop to evaluate and explore convergent technologies (nanoscience and nanotechnology, biotechnology and biomedicine, information technology, and cognitive science) for improving human cognition and communication, it was natural to start with a top-down systems engineering approach.

One of the first questions to be asked is what is meant by improvement. In sensor systems engineering, improvement covers a wide range of issues such as performance, cost, power and cooling, weight and volume, reliability, and supportability. The ranking of these issues depends on the mission for the system in question and on the sensor platform. For example, a surveillance radar system on an

aircraft has much more emphasis on the power and cooling issues than does a ground-based radar system.

Improvement has many facets in the context of the Army's Objective Force Warrior system for the dismounted soldier: enhanced fightability without impeding movement or action; minimal weight; efficient, reliable, and safe power; integratability; graceful degradation; trainability; minimal and easy maintenance (ultra-reliability); minimal logistics footprint; interoperability; and affordability. The prioritization of these requirements could change depending on whether the warrior is based on space, airborne, surface ship, or undersea platforms. Ideally, the adaptability of the system is high enough to cover a wide range of missions and platforms, but issues like cost can constrain this goal.

Improvement is a relative term, and improvement objectives in the case of human cognition depend on the definition of the baseline system to be improved, e.g., healthy versus injured brain. Furthermore, does one focus solely on cognition in the waking conscious state, or is the Rapid Eye Movement (REM) sleeping conscious state also included? Although recent memory, attention, orientation, self-reflective awareness, insight, and judgment are impaired in the REM sleep state, J. Allen Hobson suggests that this state may be the most creative one, in which the chaotic, spontaneous recombination of cognitive elements produces novel configurations of new information resulting in new ideas (Hobson 1999).

Improvement objectives for human communication include enhancements in the following:

a) communication equipment *external* to the individual, e.g., smaller, lighter cell phones operable over more frequencies at lower power

b) information transfer *between* equipment and individual, i.e., through human-machine interface

c) communication and cognitive capabilities *internal* to the individual, e.g., communication outside the normal frequency bands for human vision and hearing.

If one reviews the evolution of cognitive and communication enhancement for the dismounted soldier during the last several decades, improvements in equipment *external* to the soldier and the human-machine interface predominate. For example, Raytheon is developing uncooled infrared imagers for enhanced night vision, a tactical visualization module to enable the visualization of a tactical situation by providing realtime video, imagery, maps, floor plans, and "fly-through" video on demand, and GPS and antenna systems integrated with the helmet or body armor. Other external improvements being developed by the Department of Defense include wearable computers, ballistic and laser eye protection, sensors for detection of chemical and biological warfare agents, and smaller, lighter, and more efficient power sources. Improvements that would be inside the individual have been investigated as well, including a study to enhance night vision by replacing the visual chromophores of the human eye with ones that absorb in the infrared, as well as the use of various drugs to achieve particular states of consciousness.

The convergent technologies of nanoscience and nanotechnology, biotechnology and biomedicine, information technology, and cognitive science have the potential to accelerate evolutionary improvements in cognition and communication *external*

to the individual and the human-machine interface, as well as enable revolutionary improvements *internal* to the individual. The recent workshop on nanoscience for the soldier identified several potential internal improvements to enhance soldier performance and to increase soldier survivability: molecular internal computer, sensory, and mechanical enhancement; active water reclamation; short-term metabolic enhancement; and regeneration/self-healing (Army Research Laboratory 2001).

The trend in sensor systems is towards the integrated, wide band, multifunction sensor suite, in which processor/computer functions are extended into the sensing elements so that digitization occurs as early as possible in the sensing process. This type of sensor architecture enables a very high degree of adaptability and performance. However, one still has to trade the pros and cons of handling the increasing torrent of bits that results from digitizing closer to the sensor's front-end. For example, the power consumption associated with digitization can be an important consideration for a given platform and mission.

Improvements in human cognition and communication will also follow a path of higher integration and increased functionality. The exciting prospect is that the convergent technologies encompass the three major improvement paths: external, human-machine interface, and internal. This breadth should make it possible to pursue a more complete system solution to a particular need. If better night vision is desired, the convergent technologies could make it possible to trade a biological/chemical approach of modifying the photoreceptors in the eye, a micro/nano-optoelectronic imager external to the eye, or a hybrid of the two. Memory enhancement is an important element of improving human cognition, and perhaps convergent technologies could be used to build on work that reports using external electrical stimulation (Jiang, Racine, and Turnbull 1997) or infusion of nerve growth factor (Frick et al. 1997) to improve/restore memory in aged rats.

Sensor systems have benefited enormously from architectures inspired by the understanding of human cognition and communication. The possibility exists for sensor system engineering to return the favor by working in concert with the convergent technologies of nanoscience and nanotechnology, biotechnology and biomedicine, information technology, and cognitive science.

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CAN NANOTECHNOLOGY DRAMATICALLY AFFECT THE ARCHITECTURE OF FUTURE COMMUNICATIONS NETWORKS?

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We live in an era of astounding technological transformation — the Information Revolution — that is as profound as the two great technological revolutions of the past — the Agricultural and Industrial Revolutions. All around us are now familiar technologies whose very existence would have seemed extraordinary just a generation ago: cellular telephones, the optical fiber telecommunications backbone, the Internet, and the World Wide Web. All of the underlying technologies of the Information Age are experiencing exponential growth in functionality due to decreasing size and cost of physical components — similar to Moore's Law in silicon-integrated electronics technology. In the next decade, the size scale of many communications and computing devices — such as individual transistors — is predicted to decrease to the dimension of nanometers; where fundamental limits may slow down, single device functionality will increase. Before these fundamental limits are even attained, however, we must address the difficult assembly and interconnection problems with a network of millions of small devices tied together to provide the increased functionality at lower cost. If the interconnection problem is solved and if the cost of physical elements is dramatically reduced, the architectures of future communications networks — and the Internet itself — can be dramatically changed. In order for this to happen, however, we must have a breakthrough in our ability to deal with the statistical nature of devices in the simulation and design of complex networks on several levels.

Fundamental Limits to Individual Devices

Communications and computing rely ultimately on individual devices such as transistors, optical switching elements, memory elements, and detectors of electrical, optical, and radio signals. These devices are linked into physical modules like integrated circuits that perform the necessary functions or computations needed for the communications network or computer. For the last two decades, the trends of technology have dramatically decreased the size and power requirements of individual elements so that they can be integrated into a single complex package, thus reducing parts needed, space, and cost of functional modules such as communications receivers. I expect that these trends will continue, using what we have learned from nanotechnology research, until either fundamental physical limits to the individual devices are reached, or which is more likely, until we hit a new bottleneck of how to design and achieve the interconnection of these devices. When devices approach the nanometer scale, they will no longer be identical but will have a statistical distribution of characteristics: for example, in a 10 nm channel length transistor, the number of dopant atoms will be in the tens or hundreds and vary from transistor to transistor produced in an identical way, due to the random nature of the dopant diffusion process. This means that there will necessarily be a statistical variation of turn-on voltages, break-down voltages, channel conductivity, and so forth.

The Interconnection Problem

The engineering research of the next decade will most likely bring to fruition the integration of different functionalities on a single small platform, such as compact electro-photonic modules using engineered photonic bandgap structures to reduce the size of optical modulation-demodulation elements. I expect that the newest integration architectures will necessarily include fully three-dimensional circuits and up to a million or so "zero cost" single devices. These integrated modules will, in themselves, be complex networks of individual elements, each element type described by a statistical distribution of characteristics. We will need a breakthrough in the methods of integrated circuit simulation and design in order to deal with the complexity of designing these modules and to deal with the latency of signals travelling across long paths or through many connections. Right now, the simulation and design software for merely pure electronic integrated circuits, assuming that each element type is identical, is a major bottleneck in the production of application-specific integrated circuits (ASICS). One possibility in the far future is to harness the methods of directed self-assembly of the network of devices, much as our brain manages to learn from its environment how to assemble the synapses between neurons. We are not even close today.

Future Communications Network Architectures

As extremely small and low-cost communications modules are developed, certainly personal access networks — the equipment used by an individual to communicate with his or her near surroundings and to gain access to larger area local area networks and ultimately to the global wide area communications networks of the future — will become ubiquitous. These will mostly be wireless ad hoc networks, since people are mobile. Local area networks, for example, campus or in-building networks with range below one km, will be ubiquitous as well, whether wireless or wireline, depending on deployment costs. But how will the dramatic reduction of cost of the physical infrastructure for communications equipment affect the major communication long haul or wide area networks? Currently, the architectures of cross-continental or undersea or satellite communications systems are determined not only by the cost of components but by the costs associated with deployment, provisioning, reconfiguration, protection, security, and maintenance. The simulation and design tools used for complex wide area networks are in their infancy, as are the simulation and design tools for the integrated modules of which they are comprised. We need a breakthrough in simulation and design techniques. As the costs of the physical hardware components for wide area networks come down, the deployment costs will not fall as much, due to the power requirements needed in wide area systems, and this and the complexity of network management will probably determine network architectures. For example, the complexity of managing security and quality of service in a nationwide ad hoc wireless network comprised of billions of only small, low power base stations is enormous. Thus it is much more likely to have hierarchies of scale in networks, first personal, then local, and then medium range, culminating in a backbone network similar to what we have today. Again, we may be able to learn much from how biological networks configure themselves as we develop self-configuring, self-protecting, and self-monitoring networks.

SPATIAL COGNITION AND CONVERGING TECHNOLOGIES

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This paper explores aspects of spatial cognition and converging technologies following five themes:

1. Nano-Bio-Info-Cognitive technology (NBIC) and improving learning
2. Enhancing sensory and cognitive capabilities in the spatial domain
3. NBIC and improving human-machine interfaces
4. Suggestions about what should be done
5. Expected outcomes

NBIC and Improving Learning

What will NBIC allow us to achieve in the learning domain that we cannot achieve now?

The effects of NBIC may be

- improved knowledge of brain functioning and capabilities
- new learning domains such as immersive virtual environments
- more widespread use of nonvisual experiences for solving spatial problems
- examining sensory substitution as a way to enhance learning .

Let us briefly examine how these might occur.

Improving Knowledge of Brain Functioning and Capabilities: Place Cell Analysis.

Advances in Magnetic Resonance Imagery (MRI) have given some promise for tracking what parts of the brain are used for what functions. Opinions differ regarding the value of this technology, but much of the negative criticism is directed towards identifying which parts of the brain appear to be used for emotions such as love or hate, or for aesthetic reactions to concepts of beauty, danger, and fear. Somewhat less controversy is present in the spatial domain, where the 25-year-old hypothesis of O'Keefe and Nadel (1978) that the hippocampus is one's "cognitive map" (or place where spatial information is stored) is being actively investigated. Neurobiologists may be able to determine which neurons "fire" (or are excited) when spatial information relating to objects and their locations are sensed and stored. If NBIC can develop reliable place cell analysis, the process of mapping the human brain could be transformed into examining the geography of the brain. To do this in a thorough manner, we need to know more about spatial cognition, including understanding spatial concepts, spatial relations, spatial thinking, and spatial reasoning.

Within the domains of spatial thinking and reasoning — domains that span all scales of science and technology from the nano scale to a universe-wide scale — there is enormous potential for improving our understanding of all facets of the spatial domain. Spatial thinking and reasoning are dominated by perceptualizations, which are the multisensory expansion of visualization. The major processes of information processing include encoding of sensed experiences, the internal manipulation of sensed information in working memory, the decoding of manipulated information, and the use of the results in the decision-making and

choice processes involved in problem-solving and spatial behavior. According to Golledge (2002), thinking and reasoning spatially involves

- Understanding the effects of scale
- Competently mentally transforming perceptions and representations among different geometric dimensions (e.g., mentally expanding 1-dimensional traverses or profiles to 2-D or 3-D configurations similar to that involved in geological mapping, or reducing 3-D or 4-D static or dynamic observations to 2-D formats for purposes of simplification or generalization (as when creating graphs, maps, or images)
- Comprehending different frames of reference for location, distance estimation, determining density gradients, calculating direction and orientation, and other referencing purposes (e.g., defining coordinates, vectors, rasters, grids, and topologies)
- Being capable of distinguishing spatial associations among point, line, area, and surface distributions or configurations
- Exercising the ability to perform spatial classification (e.g., regionalization)
- Discerning patterns in processes of change or spread (e.g., recognizing patterns in observations of the spatial spread of AIDS or city growth over time)
- Revealing the presence of spatial and nonspatial hierarchies

Each of the above involves sensing of phenomena and cognitive processing to unpack embedded detail. It should also be obvious that these perceptual and cognitive processes have their equivalents in information technology (IT), particularly with respect to creating, managing, and analyzing datasets. While we are creating multiple terabytes of data each day from satellites, from LIght Detection And Ranging (LIDAR), from cameras, and from visualizations, our technology for dealing with this data — particularly for dynamic updating and realtime analysis — lags somewhat, even in the most advanced systems currently invented. Even in the case of the most efficient data collector and analyzer ever developed, the human mind, there is still a need to simplify, summarize, generalize, and represent information to make it legible. The activities required to undertake this knowledge acquisition process are called education, and the knowledge accumulation resulting from this exposure is called learning. Thus, if NBIC can empower spatial thinking and reasoning, it will promote learning and knowledge accumulation among individuals and societies, and the results will have impact the entire spatial domain. (Note, there is a National Research Council committee on spatial thinking whose report is due at the end of 2002.)

To summarize, spatial thinking is an important part of the process of acquiring knowledge. In particular, spatial knowledge, defined as the product of spatial thinking and reasoning (i.e., defined as cognitive processes) can be characterized as follows:

- Spatial thinking and reasoning do not require perfect information because of the closure power of cognitive processes such as imaging, imagining,

interpolating, generalizing, perceptual closure, gestalt integration, and learning

- Spatial metaphors are being used — particularly in IT related database development and operation — but it is uncertain whether they may or may not be in congruence with equivalent cognitive functioning.
- Spatial thinking has become an important component of IT. IT has focused on visualization as a dominant theme in information representation but has paid less attention to other sensory modalities for its input and output architectures; more emphasis needs to be given to sound, touch, smell, gaze, gesture, emotion, etc. (i.e., changing emphasis from visualizations to perceptualizations).

New Learning Domains

One specific way that NBIC developments may promote learning is by enhancement of virtual systems. In geography and other spatial sciences, learning about places other than one's immediate environment is achieved by accessing secondary information, as in books, maps, images, and tables. In the future, one may conceive of the possibility that all place knowledge could be learned by primary experience in immersive virtual environments. In fact, within 20 years, much geospatial knowledge could be taught in immersive virtual environments (VE) labs. This will require

- solution of the space sickness or motion sickness problems sometimes associated with immersion in VE
- quick and immediate access to huge volumes of data — as in terabytes of data on a chip — so that suitably real environments can be created
- adoption of the educational practice of "learning by doing"
- major new development of hardware and virtual reality language (VRL) software
- conviction of teachers that use of VE labs would be a natural consequence of the educational premise that humans learn to think and reason best in the spatial domain by directly experiencing environments.
- Investigation of which types of learning experiences are best facilitated by use of VE.

Using More Nonvisual Methods

Because of the absence of geography in many school curricula in the United States, many people have severely restricted access to (and understanding of) representations of the environment (for example, maps and images) and more abstract concepts (including spatial concepts of hierarchy and association or adjacency displayed by maps or data represented only in tables and graphs) that are fundamental in education and daily life. Representations of the geographic world (maps, charts, models, graphs, images, tables, and pictures) have the potential to provide a rich array of information about the modern world. Learning from spatialized representations provides insights into layout, association, adjacency, and other characteristics that are not provided by other learning modes. But, electronic spatial representations (maps and images) are not accessible to many groups who

lack sight, training, or experience with computerized visualizations, thus contributing to an ever-widening digital divide. With new technological developments, such as the evolution from textual interfaces to graphically based Windows environments, and the increasing tendencies for website information to be restricted to those who can access visualizations and images, many people are being frustrated in their attempts to access necessary information — even that relevant to daily life, such as weather forecasts.

When viewing representations of the geographic world, such as a map on a computer screen, sight provides a gestalt-like view of information, allowing the perception of the synoptic whole and almost simultaneously recognizing and integrating its constituent parts. However, interacting with a natural environment is in fact a multi-modal experience. Humans engage nearly all of their sensory modalities when traversing space. Jacobson, Rice, Golledge and Hegarty (2002) summarize recent literature relating to non-visual interfaces. They suggest that, in order to attend to some of this multisensory experience and to provide access to information for individuals with restricted senses, several research threads can be identified for exploring the presentation of information multimodally. For example, information in science and mathematics (such as formulae, equations, and graphs) has been presented through auditory display (e.g., hearing a sine wave) and through audio-guided keyboard input (Gardner et al. 1998; Stevens et al. 1997). Mynatt (1977) has developed a tonal interface that allows users without vision to access Windows-style graphical user interfaces. Multimodal interfaces are usually developed for specialist situations where external vision is not necessarily available, such as for piloting and operating military aircraft (Cohen and Wenzel 1995; Cohen and Oviatt 1995; Rhyne and Wolf 1993).

Jacobson et al. also point out that abstract sound variables have been used successfully for the presentation of complex multivariate data. Parkes and Dear (1990) incorporated "sound painting" into their tactual-auditory information system (NOMAD) to identify gradients in slope, temperature, and rainfall. Yeung (1980) showed that seven chemistry variables could be presented through abstract sound and reported a 90% correct classification rate prior to training and a 98% correct response rate after training. Lunney and Morrison (1981) have shown that sound graphs can convey scientific data to visually impaired students. Sound graphs have also been compared to equivalent tactual graphs; for example, Mansur et al. (1985) found comparable information communication capabilities between the two media, with the auditory displays having the added benefit of being easier to create and quicker to read. Recent research has represented graphs by combining sound and brailled images with the mathematical formula for each graph being verbally presented while a user reads the brailled shape. Researchers have investigated navigating the Internet World Wide Web through audio (Albers 1996; Metois and Back 1996) and as a tool to access the structure of a document (Portigal and Carey 1994). Data sonification has been used to investigate the structure of multivariate and geometric data (Axen and Choi 1994; Axen and Choi 1996; Flowers et al. 1996), and auditory interfaces have been used in aircraft cockpits and to aid satellite ground control stations (Albers 1994; Ballas and Kieras 1996; Begault and Wenzel 1996). But while hardware and software developments have shown "proof of concept," *there appear to be few successful implementations of the results for*

general use (except for some gaming contexts) and no conclusive behavioral experiments to evaluate the ability of the general public or specialty groups (e.g., the vision-impaired) to use these innovations to interpret on screen maps, graphics, and images.

Thus, while Jacobson et al. (2002) have illustrated that multimodal interfaces have been explored within computer science and related disciplines (e.g., Delclos and Hartman 1993; Haga and Nishino 1995; Ladewski 1996; Mayer and Anderson 1992; Merlet, Nadalin, Soutou, Lapujade, and Ravat 1993; Morozov 1996; Phillips 1994; Stemler 1997; Hui et al. 1995; and others), and a number of researchers have looked at innovative interface mediums such as gesture, speech, sketching, and eye tracking (e.g., Ballas and Kieras 1996; Briffault and Denis 1996; Dufresne et al. 1995; Schomaker et al. 1995; Taylor et al. 1991), they also claim that only recently are such findings beginning to have an impact upon technology for general education, a view shared by Hardwick et al. (1996; 1997).

In summary, extrapolating from this example, one can assume that developments in NBIC will impact the learning activities of many disciplines by providing new environments for experience, by providing dynamic realtime data to explore with innovative teaching methods, and (if biotechnology continues to unpack the secrets of the brain and how it stores information as in place cell theory), the possibility of direct human-computer interaction for learning purposes may all be possible. Such developments could

- enhance the process of spatial learning by earlier development of the ability to reason abstractly or to more readily comprehend metric and nonmetric relations in simple and complex environments
- assist learning by discovering the biotechnological signatures of phenomena and discovering the place cells where different kinds of information are stored, and in this way enhance the encoding and storage of sensed information
- where functional loss in the brain occurs (e.g., if loss of sight leaves parts of the brain relatively inactive), to find ways to use the cells allocated to sight to be reallocated to other sensory organs, thus improving their functioning capabilities.
- Representations of the geographic world (maps, charts, models, graphs, images, tables, and pictures) have the potential to provide a rich array of information about the modern world.
- Learning from spatialized representations provides insights into layout, association, adjacency, and other spatial characteristics that are not provided by other learning modes.
- However, interacting with a natural environment is in fact a multimodal experience. Humans engage nearly all of their sensory modalities when traversing or experiencing space.

Given the dominance of computer platforms for representing information and the overwhelming use of flat screens to display such information, there is reason to believe that multimodal representations may not be possible until alternatives to 2-D screen surfaces have been developed for everyday use. The reasons for moving

beyond visualization on flat screens are compelling and are elaborated on later in this chapter.

Enhancing Sensory and Cognitive Capabilities in the Spatial Domain

How can we exploit developments in NBIC to enhance perceptual and cognitive capabilities across the life span, and what will be the types of developments needed to achieve this goal?

To enhance sensory and cognitive capabilities, a functional change in the way we encode information, store it, decode it, represent it, and use it may be needed. Much of the effort in Information Technology has been directed towards developing bigger and bigger databases that can be used on smaller and smaller computers. From satellites above we get terabytes of data (digitized records of the occurrence of phenomena), and we have perhaps outgrown our ability to examine this data. As nanotechnology and IT come into congruence, the terabytes of data being stored in boxes will be stored on chips and made accessible in real time via wearable and mobile computers, and even may be fed into smart fabrics woven into the clothes we wear. But just how well can we absorb, access, or use this data? How much do we need to access? And how best *can* we access it and use it? The question arises as to how we can exploit human perception and cognition to best help in this process, and the answer is to find out more about these processes so that they can be enhanced. Examples of questions to be pursued include the following:

- How can we enhance the sensory and cognitive aspects of human wayfinding for use in navigating in cyberspace?
- What particular sensory and cognitive capabilities are used in the field, and how do we enhance them for more effective fieldwork with wearable and mobile computers (e.g., for disaster responses)?
- How do we solve problems of filtering information for purposes of representation and analysis (e.g., enhance visualizations)?
- How do we solve the problem of resolution, particularly on the tiny screens typical of wearable and field computers?
- What alternatives to visualization may be needed to promote ease of access, representation, and use of information?
- What is the best mode for data retrieval in field settings (e.g., how do we get the information we need now)?
- How can we build technology to handle realtime dynamic input from several sources, as is done by human sensory organs and the human brain?
- Will we need a totally new approach to computer design and interface architecture (e.g., abandon keyboards and mice) that will allow use of the full range of sensory and cognitive capabilities, such as audition, touch, gaze, and gesture (e.g., the use of Talking Signs® and Internet connections to access websites tied to specific locations)?

Visualization is the dominant form of human-IT interaction. This is partly because the visual sense is so dominant, particularly in the spatial domain. It is also the dominant mode for representation of analyzed data (on-screen). But visualization is but a subset of spatialization, which goes beyond the visual domain by using

everyday multimodal situations (from desktops and file cabinets to overlay and digital worlds) to organize and facilitate access to stored information. These establish a linking by analogy and metaphor between an information domain and familiar elements of everyday experience. Spatial (and specifically geographic) metaphors have been used as database organizing systems. But even everyday geospatial experiences are biased, and to enhance our sensory and cognitive abilities we need to recognize those biases and mediate them if successful initiation of everyday knowledge and experience (including natural languages) are to be used to increase human-IT interactions.

The main problem arising from these usages is simply that an assumption of general geospatial awareness is false. Basic geographic knowledge (at least in the United States) is minimal, and knowledge of even rudimentary spatial concepts like distance, orientation, adjacency, and hierarchy is flawed. Recent research in spatial cognition has revealed a series of biases that permeate naïve spatial thinking. Partly because of a result of cognitive filtering of sensed information and partly because of inevitable technical errors in data capture and representation, biases occur. Golledge (2002) has suggested that these include the following:

- conceptual bias due to improper thinking and reasoning (e.g., applying metric principles to nonmetric situations)
- perceptual biases, including misunderstandings and misconceptions of notions of symmetry, alignment, clustering, classification, closure, and so on (e.g., assuming Miami, Florida, MUST be east of Santiago, Chile, because Miami is on the east cost of North America and Santiago is on the west coast of South America) (Fig. B.1)

Figure B.1. Cognitive East/ West alignment effects.

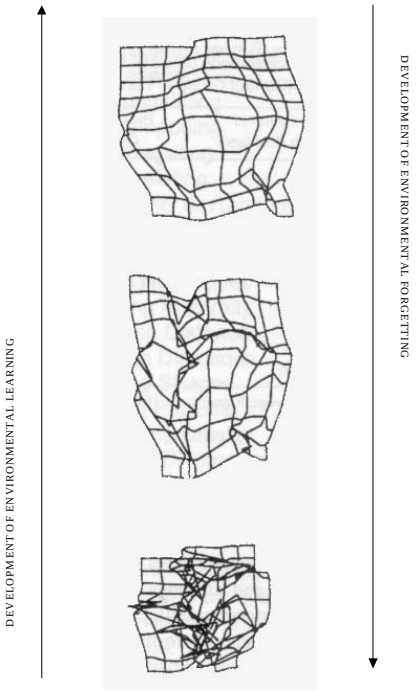

Figure B.2. Three examples of cognitive maps, of long-term residents (top), mid-term residents, (middle), and newcomers (bottom), recovered using non-metric multidimensional scaling of cognitive interpoint distances. (The exact parallel reversals for memory loss is speculative.)

- violating topological features of inclusion and exclusion when grouping (spatial) data
- assuming distance asymmetry when distance symmetry actually exists, and vice versa (e.g., different perceptions of trips to and from work)
- inappropriate use of cognitive concepts of rotation and alignment (e.g., misreading map orientation)
- cognitively overestimating shorter distances and underestimating longer distances (Stevens' Law or regression towards the mean)
- distortions in externalized spatial products (e.g., distorted cognitive maps) (Liben 1982; Fig. B.2)
- bias that results from using imprecise natural language (e.g., fuzzy spatial prepositions like "near" and "behind" that are perspective dependent). (Landau and Jackendoff 1993)

Golledge has argued that these (and other storage, processing, and externalizing biases) result in perceptual and cognitive errors in encoding, internally manipulating, decoding, and using stored information. The following are examples of the accommodations humans make to deal with these biases (incidentally developing new ones):

- making naturally occurring irregular shapes and areas regular for purposes of simplification, representation, and generalization
- mentally rotating features or distributions to fit preconceptions (e.g., vertically aligning North and South America, as shown in Figure B.1)
- imposing hierarchical orderings to clarify distributions (e.g., systems of landmarks)
- making effective rational decisions without perfect information
- cognitively generalizing from one scale to another without appropriate empirical evidence (e.g., from laboratory to real world scales)
- realizing that data collected for machine use has to be more perfect than data collected for human use.

NBIC and Improving Human-Computer Interfaces and Interactions

A key question is why won't existing interface architecture be appropriate for human-computer interaction in the future?

Existing interface architecture is still being modeled on dated technology — the typewriter keyboard and the cursor driven mouse — and not for ease of human-computer interaction. The interface concern is the most pressing problem of HCI and is its most critical part. It is the medium through which information is accessed, questions are posed, and solution paths are laid out and monitored. It is the tool with which the user manipulates and interacts with data. Interface architectures like the desktop, filing cabinet, and digital world are implemented (still) via keyboards and mice. Today's interfaces are cursor dependent and contribute significantly to creating a digital divide that impedes 8 million sight-impaired and 82 million low-vision (potential) users from freely interacting with the dominant IT of this age.

Communicating involves transferring information; to do so requires compatibility between sender and receiver. The interface architecture that controls human-computer information exchange, according to Norman (1988), must accomplish the following:

- facilitate the exchange of knowledge in the environment and knowledge in the head
- keep the interaction task simple
- ensure that operations are easy to do
- ensure correct transfer among information domains
- understand real and artificial restraints on interaction
- acknowledge existence of error and bias due to modal difficulties
- eventually standardize procedures

Thus, the interface must maximize the needs of both human user and computer.

These needs raise the question of what cutting edge hardware (e.g., rendering engines, motion tracking by head mounted display units, gaze tracking, holographic images, avatars complete with gestures, and auditory, tactual, and kinesthetic interface devices), adds to information processing? Besides the emphasis on historic input devices (keyboard and mouse), there is a similar emphasis on a dated output device, the limited domain of the flat computer screen (inherited from the TV screen of the 1930s), which is suited primarily for visualization procedures for output representation. While there is little doubt that the visual senses are the most versatile mode for the display of geospatial data and data analysis (e.g., in graph, table, map, and image mode), it is also argued that multiple modality interfaces could enrich the type, scale, and immediacy of displayed information. One of the most critical interface problems relates to the size and resolution of data displays. This will be of increasing importance as micro-scale mobile and wearable computers have to find alternatives to 2-inch square LED displays for output presentation. The reasons for moving beyond visualization on flat screens are compelling. Examples include the following:

- multimodal access to data and representations provide a cognitively and perceptually rich form of interaction

- multimodal input and output interfaces allow HC interaction when sight is not available (e.g., for blind or sight-impaired users) or when sight is an inappropriate medium (e.g., accessing onscreen computer information when driving a vehicle at high speeds)
- when absence of light or low precludes the use of sight
- when visual information needs to be augmented
- when a sense other than vision may be necessary (e.g., for recording and identifying bird calls in the field)

Nonvisual technology allows people with little or no sight to interact (e.g., using sound, touch, and force-feedback) with computers. Not only is there a need for text to speech conversion, but there is also a need to investigate the potential use of nonvisual modalities for accessing cursor-driven information displays, icons, graphs, tables, maps, images, photos, windows, menus, or other common data representations. Without such access, sight-disabled and low-sight populations are at an immense disadvantage, particularly when trying to access spatial data. This need is paramount today as home pages on the World Wide Web encapsulate so much important information in graphic format, and as digital libraries (including the Alexandria Digital Map and Image Library at the University of California, Santa Barbara) become the major storage places for multidimensional representations of spatial information.

In the near future, one can imagine a variety of new interfaces, some of which exist in part now but which need significant experimentation to evaluate human usability in different circumstances before being widely adopted. Examples of underutilized and underinvestigated technologies include the following:

- a force-feedback mouse that requires building virtual walls around on-screen features, including windows, icons, objects, maps, diagrams, charts, and graphs. The pressure-sensitive mouse allows users to trace the shape of objects or features and uses the concept of a gravity well to slip inside a virtual wall (e.g., a building entrance) to explore the information contained therein (Jacobson et al. 2002).
- vibrotactile devices (mice) that allow sensing of different surfaces (dots, lines, grates, and hachures) to explore flat, on-screen features (e.g., density shading maps and meteorological or isoline temperature maps) (O'Modhrain and Gillespie 1995; Jacobson, et al. 2002)
- use of real, digitized, or virtual sounds including speech to identify on-screen phenomena (e.g., Loomis, Golledge, and Klatzky 2001)
- avatars to express emotions or give directions by gesturing or gazing
- smart clothing that can process nearby spatial information and provide information on nearby objects or give details of ambient temperature, humidity, pollution levels, UV levels, etc.

Currently, the use of abstract sound appears to have significant potential, although problems of spatial localization of sound appear to offer a significant barrier to further immediate use. Some uses (e.g., combinations of sound and touch — NOMAD — and sound and Braille lettering — GPS Talk — are examples of

useful multimodal interfaces (e.g., Parkes and Dear 1990; Brabyn and Brabyn 1983; Sendero Group 2002). Some maps (e.g., isotherms/density shading) have proven amenable to sound painting, and researchers in several countries have been trying to equate sound and color. At present, much of the experimentation with multimodal interfaces is concentrated in the areas of video games and cartoon-like movies. Researchers such as Krygier (1994) and Golledge, Loomis, and Klatzky (1994) have argued that auditory maps may be more useful than tactual maps and may, in circumstances such as navigating in vision-obstructed environments, even prove more useful than visual maps because they don‘t require map-reading ability but rely on normal sensory experiences to indicate spatial information such as direction.

What Needs to be Done to Help NBIC Make Contributions in the Spatial Domain?

- If space is to be used as a metaphor for database construction and management, and if human wayfinding/navigation practices are to be used as models for Internet search engines, there are a host of spatial cognition research activities that need to be pursued. First there is a need for a concept-based common vocabulary. There must be a sound ontology, an understanding of spatial primitives and their derivatives, and a meaningful way to communicate with a computer using natural language and its fuzzy spatial prepositions (i.e., a common base of spatial linguistics, including a grammar).
- We need to find matches between information types and the best sensory modalities for representing and using each type of information.
- We need an educated and IT-enlightened science and engineering community that understands spatial thinking and reasoning processes.
- We need to change educational and learning practices to produce an NBIC-enlightened public and an IT-enlightened set of decision makers. Part of this need can be achieved by producing spatially aware professionals who understand and use actual or enhanced sensory and cognitive capabilities to understand and react to different situations and settings.
- We need to explore the cognitive processes used in risky decision making and use innovative IT practices to develop databases, management systems, and analytical techniques that are cognitively compatible with these processes (Montello 2001).
- We need to develop new realtime dynamic human-computer interfaces (both input and output) that facilitate collaborative decision making. This may involve building virtual environments suited for realtime collaborative image exchange and simultaneous use, analysis, modification, and representation of data, even when researchers are continents apart.
- We need to determine what dimensions of cyberspace are compatible with perceptualization and visualization, particularly in the spatial domain.
- We need to define the impacts of selecting specific scales and levels of resolution for visual or perceptual representation of information.

- We need to explore the value of changing network representations and displays of information in cyberspace to grid layout or configurational displays — the expansion from 1- to 2- or 3-dimensional information representations would facilitate a higher level of abstract thinking and reasoning to be implemented in analyzing configurational displays.
- The explosion of interfaces built upon visualization has produced too many graphic interfaces that do not maximize cognitive capabilities of users and have further disadvantaged disabled groups such as the blind or sight-impaired. This latter fact is continuing the computer alienation of aged populations, where over 70% have low vision or other sight problems. There are, according to census estimates, over 52 million disabled people in the United States. Approximately 3-4 million of these are blind, legally blind, or severely vision-impaired. A further 80+ million people have low vision. We cannot ignore these groups or exclude them from use of future technology.
- We need to determine optimal output interfaces for wearable computers that do not limit the user to visually reading complex displays (e.g., maps) on tiny screens. This carries with it the various cartographic representation problems of choosing scale, resolution, degree of simplification, generalization, and accuracy. This is not just a computer graphics problem, but a problem for cartographic theorists, empirical researchers, and researchers in spatial perception and spatial cognition, and it may involve innovative nanotechnology to build “fold-out“ or “expandable“ screens.
- There is a need to explore interfaces that can meaningfully display dynamic data at various scales and degrees of resolution.
- There is a need to examine whether nano- or biotechnology can alter the senses and cognitive capabilities of humans to enhance HCI. In particular, can nano-biotechnology enhance our tactual and auditory capabilities (e.g., sensing gloves and ear implants) to ensure that information processing becomes perceptually and cognitively less biased and error ridden?
- There is a need for distributed national learning and research networks to be developed to encourage timely transfer of information from the research to the educational domains; otherwise, the current 3-5 year lags needed for much of this transfer to take place will continue.
- As we learn more about how the mind stores data, there is a need to examine whether we can use the mind as a model to enhance efforts to build a national network of digital libraries.
- There is a need for solving problems associated with using immersive virtual environments (e.g., motion sickness) so that their real potential in research and decision making can be exploited and evaluated.
- There is a need to explore ways to increase the effectiveness of human-environment relations. This may involve
  - developing personal guidance and spatial information systems that allow people to carry with them in a wearable computer all the local

environmental information that they need to undertake daily activities (Fig. B.3)

– developing smart environments that allow people to access wireless information (e.g., infrared-based auditory signage or locally distributed servers that allow immediate access to the Internet and web pages) (Fig. B.4).

Figure B.3. Personal guidance system.

- Since environmental information is filtered through our senses and consequently is biased, individually selective, and related to stage of cognitive development, we need to know to what extent human sensing is dependent on perspective or point of view for encoding spatial relations. Attention must be paid to the roles of alignment, frames of reference, and scale or resolution (e.g., asymmetries of distance, orientation error, or locational inaccuracy), which produce information not always consistent with metric geometries and logically based algebras used to unpack information from data about the real world. Perhaps a new subjective mathematics is needed to interpret our cognitive maps.

Figure B.4. "Smart environments."

- We need to determine if knowledge of wayfinding in the real world can help us find our way in cyberspace. Spatial knowledge in humans develops from landmark route configurational understanding. Much high-order spatial knowledge in humans concerns understanding spatial relations embedded in configurational or layout knowledge, whereas much of the knowledge in IT is link- and network-based, potentially reducing its information potential by requiring human ability to integrate information obtained from specific routes in cyberspace.

There are two dominant ways for NBIC to impact the 52+ million disabled people in the United States:

1. free them from the tyranny of print and other "inaccessible" visual representations
2. help them obtain independence of travel

Enacting measures like the following will increase mobility, employability, and quality of life:

- changing computer interface architecture so that disabled groups (e.g., blind, sight impaired, dyslexic, arthritic, immobile) can access the Internet and its webpages as transparently and quickly as able-bodied people
- enabling wearable computers for use in everyday living (e.g., finding when the next bus is due or where it is now) (Fig. B.4)
- developing voice-activated personal guidance systems using GPS, GIS, and multimodal interfaces that will enable people to travel in unfamiliar environments (Fig. B.4)
- improve speech recognition for input to computers
- use infrared-based remote auditory signage systems (RASS) (e.g., talking sign technology) to facilitate wayfinding, business or object location identification, recognition of mass transit services and promotion of intermodal transfer, and to define other location-based services and information systems

Outcomes

Following are some outcomes of the integration of spatial cognition and converging NBI technologies:

- Expanding sensory and cognitive capabilities should improve learning and result in a more NBIC-enlightened public, scientists, engineers, and public policymakers.
- Developing multimodal input and output interfaces will enrich human ability to process and analyze information, covering all types of spatial information required for microscopic, global, or extraterrestrial research. It will also help to remove the rapidly growing effects of the digital divide by allowing more disabled (or otherwise disadvantaged) people to join the computer-literate population, thus improving employment possibilities and improving quality of life.

Converging NBIC technology will broaden our abilities to think "outside the box" in a variety of sensory domains, such as the following examples of convergence of NBI and spatial cognition methods:

- Natural language-driven mobile and wearable computers
- Internet search engines based on human wayfinding practices
- Smart fabrics that sense the environment and warn us of pollution levels, etc.
- Smart environments (e.g., remote auditory signage systems) that talk to us as we travel through them

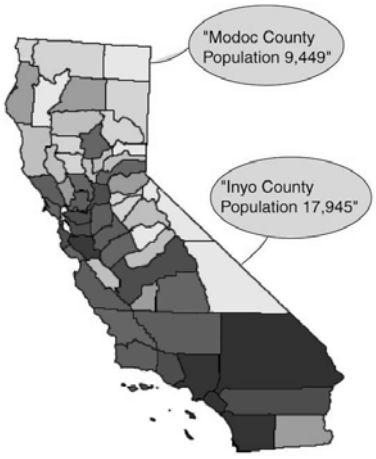

Figure B.5. Talking maps.

- GPS-based personal guidance systems that facilitate travel (e.g., tourism) in unfamiliar places
- Smart maps that explain themselves at the touch of a stylus or as a result of gaze or gesture (e.g., "You are here" maps or on-screen computer representations of data) (Fig. B.5)
- Robotic guide dogs that carry large environmental databases and can develop routes to unfamiliar places
- Smart buildings that inform about their contents and inhabitants, e.g., transit terminals (Fig. B.6).

Of particular interest are NBIC-based knowledge and devices that enhance spatial cognition used in wayfinding performance:

- Remote auditory signage (Talking Signs/Remote Infrared Auditory Signage) (at places or on vehicles, including mass transit)
- Talking fluorescent lights inside buildings such as shopping centers and transit terminals (Fig. B.7)

GPS-based guidance systems with Pointlink capabilities to locations and websites for place-based information.

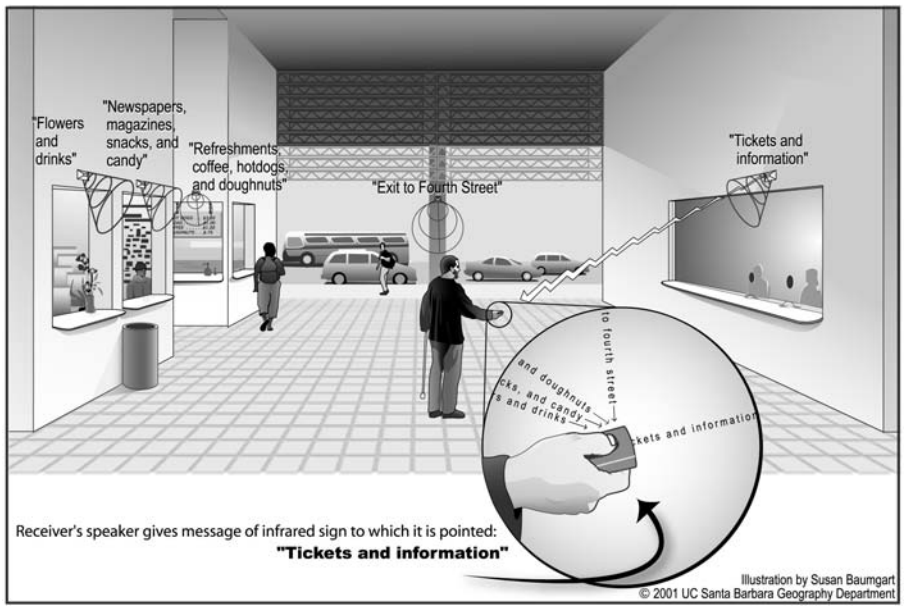

Figure B.6. Transit terminal with remote auditory signage.

Figure B.7. Talking neon lights in airport terminal.

Conclusion

The convergence of nano-, bio-, info- technology and spatial cognition research will

- broaden our ability to think outside the box
- ensure that NBI technologies are compatible with ways humans think and reason
- facilitate new product development
- help remove barriers to the natural integration of disabled and disadvantaged groups into the community, thus improving their quality of life
- provide new environments for learning
- enhance cognitive functioning by improving perceptual and cognitive capabilities
- help create less abstract and more "naturally human" computer interface architecture
- once we have learned how and where spatial information is stored in the brain (place cell analysis), this may prompt new ideas about how we think and reason

For example, eventually, the most powerful computer interface will rely on an architecture that combines geospatial metaphors with spatialization principles and

multimodal input and output devices that provide access to text, maps, images, tables, and gestures.

But there is the inevitable downside, such as the thorny ethical and legal issues of defining and maintaining appropriate levels of individual privacy and security of public or business information. But developments in NBIC are the future of humankind, and these and other unrealized problems, must — in the way of humankind — be faced and solved.

Finally, if VE can be developed in an effective way, humans will have many of the capabilities of the Star Trek holodeck. They will stroll through the Amazon jungles, trek to the North or South Pole, explore an active volcano, avalanche, or hurricane, redesign cities or parts of them, change transport systems to maximize the benefits of intelligent highways, visit drought areas, explore areas of poverty or crime, all within the safety of VE. The contribution of such systems to education, research, and decision making in the policy arena could be immense. As long as we can solve the cognition and technical problems of building and using VE, these goals may be achievable.

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VISUAL LANGUAGE AND CONVERGING TECHNOLOGIES IN THE NEXT 10-15 YEARS (AND BEYOND)

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Visual language is one of the more promising avenues to the improvement of human performance in the short run (the next 10 to 15 years) (Horn 2000b, 2000c). The current situation is one of considerable diversity and confusion as a new form of communication arises. But visual language also represents many great opportunities. People think visually. People think in language. When words and visual elements are closely intertwined, we create something new and we augment our communal intelligence.

Today, human beings work and think in fragmented ways, but visual language has the potential to integrate our existing skills to make them tremendously more effective. With support from developments in information technology, visual language has the potential for increasing human "bandwidth," the capacity to take in, comprehend, and more efficiently synthesize large amounts of new information. It has this capacity on the individual, group, and organizational levels. As this convergence occurs, visual language will enhance our ability to communicate, teach, and work in fields such as nanotechnology and biotechnology.

Definition

Visual language is defined as the tight integration of words and visual elements and has characteristics that distinguish it from natural languages as a separate communication tool as well as a distinctive subject of research. It has been called visual language, although it might well have been called visual-verbal language.

A preliminary syntax, semantics, and pragmatics of visual language have been described. (Horn 1998) Description of, understanding of, and research on visual language overlap with investigations of scientific visualization and multimedia.

History

The tight integration of words and visual elements has a long history (Horn 1998, Chapter 2). Only in the last 50 years, with the coming together of component visual

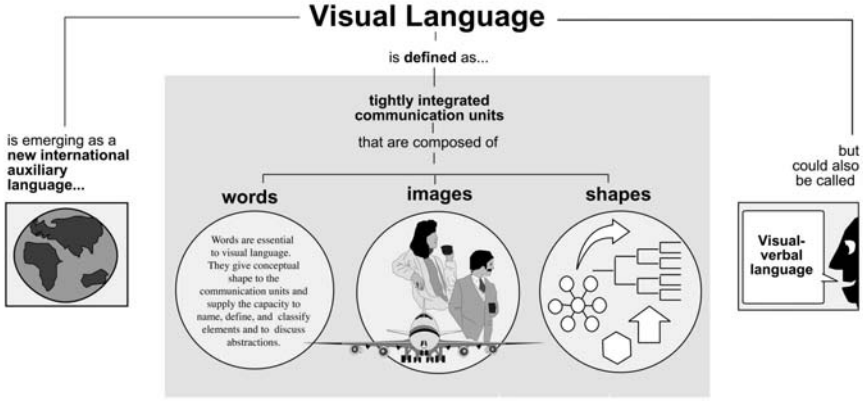

Figure B.8. Defining visual language.

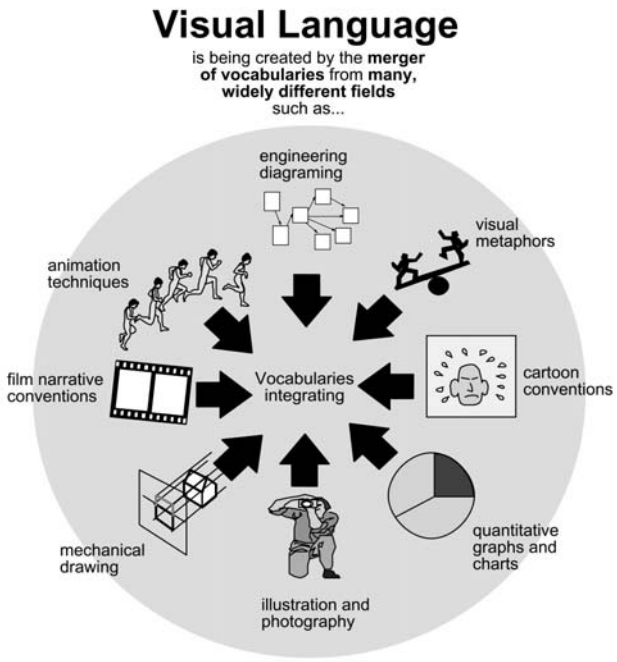

Figure B.9. Creation of visual language.

vocabularies from such widely separate domains as engineering diagramming technologies developed in medical illustration and hundreds of expressive visual conventions from the world of cartooning, has something resembling a full, robust visual-verbal language appeared (Tufte 1983, 1990).

Its evolution has been rapid in the past 10 years, especially with the confluence of scientific visualization software; widespread use of other quantitative software that permits the creation of over one hundred quantitative graphs and charts with the push of a single function key; and the profusion of multimedia presentation software, especially PowerPoint which, it is said, has several million users a day.

The Promise of *More Effective Communication*

There is widespread understanding that visual-verbal language enables forms and efficiencies of communication that heretofore have not been possible. For example, improvements in human performance from 23% to 89% have been obtained by using integrated visual-verbal stand-alone diagrams. In this case, stand-alone diagrams refer to diagrams that have all the verbal elements necessary for complete understanding without reading text elsewhere in a document (Chandler and Sweller 1991; Mayer 2001; Horton 1991).

There are several key advantages of the emerging visual-verbal language:

1. **It facilitates representation.** This new language facilitates presentation of complex, multidimensional visual-verbal thought, and — with multimedia tools — can incorporate animation, as well. Researchers and scholars are no longer constrained by the scroll-like thinking of endless paragraphs of text.

2. **It facilitates big, complex thoughts**. Human cognitive effectiveness and efficiency is constrained by the well-known limitations of working memory that George Miller identified in 1957 (Miller 1957). Large visual displays have for some time been known to help us overcome this bandwidth constraint. But only since the recent advances in visual language have we been able to imagine a major prosthesis for this human limitation. The prosthesis consists of a suite of visual language maps. This visual-verbal language (together with computer-based tools) may eliminate the major roadblocks to thinking and communicating big, complex thoughts, i.e., the problem of representing and communicating mental models of these thoughts efficiently and effectively.

   This especially includes the so-called "messy" (or "wicked" or "ill-structured") problems (Horn 2001a). Problems have straightforward solutions; messy problems do not. They are

   – more than complicated and complex; they are ambiguous
   – filled with considerable uncertainty — even as to what the conditions are, let alone what the appropriate actions might be
   – bounded by great constraints and tightly interconnected economically, socially, politically, and technologically

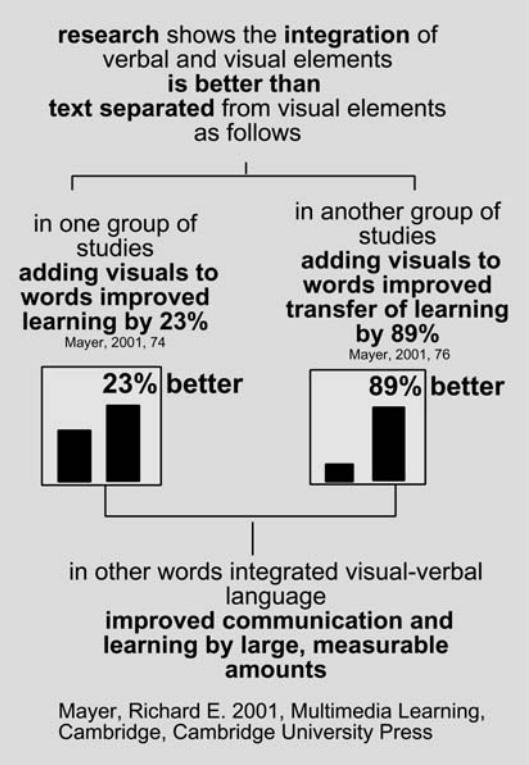

Figure B.10. Enhancing learning through visual language.

- seen differently from different points of view and quite different worldviews
- comprised of many value conflicts
- often alogical or illogical

These kinds of problems are among the most pressing for our country, for the advancement of civilization, and for humanity; hence, the promise of better representation and communication of complex ideas using visual-verbal language constructs has added significance.

Premises Regarding Visual Language

A deep understanding of the patterns of visual language will permit the following:

- more rapid, more effective interdisciplinary communication
- more complex thinking, leading to a new era of thought
- facilitation of business, government, scientific, and technical productivity
- potential breakthroughs in education and training productivity
- greater efficiency and effectiveness in all areas of knowledge production and distribution
- better cross-cultural communication

Readiness for Major Research and Development

A number of major jumping-off research platforms have already been created for the rapid future development of visual language: the Web; the ability to tag content with XML; database software; drawing software; a fully tested, widely used content-organizing and tagging system of structured writing known as Information Mapping® (Horn 1989); and a growing, systematic understanding of the patterns of visual-verbal language (Kosslyn 1989, 1994; McCloud 1993; Horton 1991; Bertin 1983).

Rationale for the Visual Language Projects

A virtual superhighway for rapid development in visual language can be opened, and the goals listed above in the premises can be accomplished, if sufficient funds over the next 15 years are applied to the creation of tools, techniques, and taxonomies, and to systematically conducting empirical research on effectiveness and efficiency of components, syntax, semantics, and pragmatics of this language. These developments, in turn, will aid the synergy produced in the convergence of biotechnology, nanotechnology, information technology, and cognitive science.

Goals of a Visual-Verbal Language Research Program

A research program requires both bold, general goals and specific landmarks along the way. A major effort to deal with the problem of increasing complexity and the limitations of our human cognitive abilities would benefit all human endeavors and could easily be focused on biotechnology and nanotechnology as prototype test beds. We can contemplate, thus, the steady, incremental achievement of the following goals as a realistic result of a major visual language program:

1. **Provide policymakers with comprehensive visual-verbal models**. The combination of the ability to represent complex mental models and the ability to collect realtime data will provide sophisticated decision-making tools for social policy. Highly visual cognitive maps will facilitate the management of and navigation through major public policy issues. These maps provide patterned abstractions of policy landscapes that permit the decisionmakers and their advisors to consider which roads to take within the wider policy context. Like the hundreds of different projections of geographic maps (e.g., polar or Mercator), they provide different ways of viewing issues and their backgrounds. They enable policymakers to drill down to the appropriate level of detail. In short, they provide an invaluable information management tool.
2. **Provide world-class, worldwide education for children.** Our children will inherit the results of this research. It is imperative that they receive the increased benefits of visual language communication research as soon as it is developed**.** The continued growth of the Internet and the convergence of intelligent visual-verbal representation of mental models and computer-enhanced tutoring programs will enable children everywhere to learn the content and skills needed to live in the 21st century. But this will take place only if these advances are incorporated into educational programs as soon as they are developed.
3. **Achieved large breakthroughs in scientific research.** The convergence of more competent computers, computer-based collaborative tools, visual representation breakthroughs, and large databases provided by sensors will enable major improvements in scientific research. Many of the advances that we can imagine will come from interdisciplinary teams of scientists, engineers, and technicians who will need to become familiar rapidly with fields that are outside of their backgrounds and competencies. Visual language resources (such as the diagram project described below) will be required at all levels to make this cross-disciplinary learning possible. This could be the single most important factor in increasing the effectiveness of nano-bio-info teams working together at their various points of convergence.
4. **Enrich the art of the 21st century.** Human beings do not live by information alone. We make meaning with our entire beings: emotional, kinesthetic, and somatic. Visual art has always fed the human spirit in this respect. And we can confidently predict that artistic communication and aesthetic enjoyment in the 21st century will be enhanced significantly by the scientific and technical developments in visual language. Dynamic visual-verbal murals and art pieces will become one of the predominant contemporary art forms of the century, as such complex, intense representation of meaning joins abstract and expressionistic art as a major artistic genre. This has already begun to happen, with artists creating the first generation of large visual language murals (Horn 2000).
5. **Develop smart, visual-verbal thought software.** The convergence of massive computing power, thorough mapping of visual-verbal language patterns, and advances in other branches of cognitive science will provide for an evolutionary leap in capacity and in multidimensionality of thought processes. Scientific visualization software in the past 15 years has led the

way in demonstrating the necessity of visualization in the scientific process. We could not have made advances in scientific understanding in many fields without software that helps us convert "firehoses of data" (in the vivid metaphor of the 1987 National Science Foundation report on scientific visualization) into visually comprehensible depictions of *quantitative* phenomena and simulations. Similarly, every scientific field is overwhelmed with *tsunami*s of new *qualitative* concepts, procedures, techniques, and tools. Visual language offers the most immediate way to address these new, highly demanding requirements.

6. **Open wide the doors of creativity.** Visualization in scientific creativity has been frequently cited. Einstein often spoke of using visualization on his *gedanken* experiments. He saw in his imagination first and created equations later. This is a common occurrence for scientists, even those without special training. Visual-verbal expression will facilitate new ways of thinking about human problems, dilemmas, predicaments, emotions, tragedy, and comedy. "The limits of my language are the limits of my world," said Wittgenstein. But it is in the very nature of creativity for us to be unable to specify what the limits will be. Indeed, it is not always possible to identify the limits of our worlds until some creative scientist has stepped across the limit and illuminated it from the other side.

Researchers in biotechnology and nanotechnology will not have to wait for the final achievement of these goals to begin to benefit from advances in visual language research and development. Policymakers, researchers, and scholars will be confronting many scientific, social, ethical, and organizational issues; each leap in our understanding and competence in visual language will increase our ability to deal with these kinds of complex issues. As the language advances in its ability to handle complex representation and communication, each advance can be widely disseminated because of the modular nature of the technology.

Major Objectives Towards Meeting Overall Goals of Visual-Verbal Language Research

The achievement of the six goals described above will obviously require intermediate advances on a number of fronts to achieve specific objectives:

1. **Diagram an entire branch of science with stand-alone diagrams.** In many of the newer introductory textbooks in science, up to one-third of the total space consists of diagrams and illustrations. But often, the function of scientific diagrams in synthesizing and representing scientific processes has been taken for granted. However, recent research cited above (Mayer 2001, Chandler and Sweller 1991) has shown how stand-alone diagrams can significantly enhance learning. Stand-alone diagrams do what the term indicates: everything the viewer needs to understand the subject under consideration is incorporated into one diagram or into a series of linked diagrams. The implication of the research is that the text in the other two thirds of the textbooks mentioned above should be distributed into diagrams.

   "Stand-alone" is obviously a relative term, because it depends on previous learning. One should note here that automatic prerequisite linkage is one of the easier functions to imagine being created in software packages designed

to handle linked diagrams. One doesn't actually have to take too large a leap of imagination to see this as achievable, as scientists are already exchanging PowerPoint slides that contain many diagrams. However, this practice frequently does not take advantage of either the stand-alone or linked property.

Stand-alones can be done at a variety of styles and levels of illustration. They can be abstract or detailed, heavily illustrated or merely shapes, arrows, and words. They can contain photographs and icons as well as aesthetically pleasing color.

Imagine a series of interlinked diagrams for an entire field of science. Imagine zooming in and out — always having the relevant text immediately accessible. The total number of diagrams could reach into the tens of thousands. The hypothesis of this idea is that such a project could provide an extraordinary tool for cross-disciplinary learning. This prospect directly impacts the ability of interdisciplinary teams to learn enough of each other's fields in order to collaborate effectively. And collaboration is certainly the key to benefiting from converging technologies.

Imagine, further, that using and sharing these diagrams were *not* dependent on obtaining permission to reproduce them, which is one of the least computerized, most time-consuming tasks a communicator has to accomplish these days. Making permission automatic would remove one of the major roadblocks to the progress of visual language and a visual language project.

Then, imagine a scientist being able to send a group of linked, stand-alone diagrams to fellow scientists.

2. **Create "periodic" table(s) of types of stand-alone diagrams.** Once we had tens of thousands of interlinked diagrams in a branch of science, we could analyze and characterize all the components, structures, and functions of all of the types of diagrams. This would advance the understanding of "chunks of thinking" at a fine-grained level. This meta understanding of diagrams would also be a jumping-off point for building software tools to support further investigations and to support diagramming of other branches of science and the humanities.
3. **Automatically create diagrams from text.** At the present moment, we do not know how to develop software that enables the construction from text of a wide variety of kinds of elaborate diagrams. But if the stand-alone diagrams prove as useful as they appear, then an automatic process to create diagrams, or even just first drafts of diagrams, from verbal descriptions will turn out to be extremely beneficial. Imagine scientists with new ideas of how processes work speaking to their computers and the computers immediately turning the idea into the draft of a stand-alone diagram.
4. **Launch a project to map the human cognome.** In the Converging Technologies workshop I suggested that we launch a project that might be named "Mapping the Human Cognome." If properly conceived, such a project would certainly be the project of the century. If the stand-alone diagram project succeeds, then we would have a different view of human thought chunks. Since human thought-chunks can be understood as fundamental building blocks of the human cognome, the rapid achievement

of stand-alone diagrams for a branch of science could, thus, be regarded as a starting point for at least one major thrust of the Human Cognome Project (Horn 2002c).

5. **Create tools for collaborative mental models based on diagramming.** Ability to come to rapid agreement at various stages of group analysis and decision-making with support from complex, multidimensional, visual-verbal murals is becoming a central component of effective organizations. This collaborative problem-solving, perhaps first envisioned by Douglas Engelbart (1962) as augmenting human intellect, has launched a vibrant new field of computer-supported collaborative work (CSCW). The CSCW community has been facilitating virtual teams working around the globe on the same project in a 24/7 asynchronous timeframe. Integration of (1) the resources of visual language display, (2) both visual display hardware and software, and (3) the interactive potential of CSCW offers possibilities of great leaps forward in group efficiency and effectiveness.
6. **Crack the unique address dilemma with fuzzy ontologies.** The semantic web project is proceeding on the basis of creating unique addresses for individual chunks of knowledge. Researchers are struggling to create "ontologies," by which they mean hierarchical category schemes, similar to the Dewey system in libraries. But researchers haven't yet figured out really good ways to handle the fact that most words have multiple meanings. There has been quite a bit of progress in resolving such ambiguities in machine language translation, so there is hope for further incremental progress and major breakthroughs. An important goal for cognitive scientists will be to produce breakthroughs for managing the multiple and changing meanings of visual-verbal communication units on the Web in real time.
7. **Understand computerized visual-verbal linkages.** Getting computers to understand the linkage between visual and verbal thought and their integration is still a major obstacle to building computer software competent to undertake the automatic creation of diagrams. This is likely to be less of a problem as the stand-alone diagram project described above (objective #1) progresses.
8. **Crack the "context" problem.** In meeting after meeting on the subject of visual-verbal language, people remark at some point that "it all depends on the context." Researchers must conduct an interdisciplinary assault on the major problem of carrying context and meaning along with local meaning in various representation systems. This may well be accomplished to a certain degree by providing pretty good, computerized common sense. To achieve the goal of automatically creating diagrams from text, there will have to be improvements in the understanding of common sense by computers. The CYC project, the attempt to code all of human common sense knowledge into a single database — or something like it — will have to demonstrate the ability to reason with almost any subject matter from a base of 50 million or more coded facts and ideas. This common-sense database must somehow be integrally linked to visual elements.

Conclusion

It is essential to the accelerating research in the fields of nanotechnology, biotechnology, information technology, and cognitive science that we increase our understanding of visual language. In the next decade, we must develop visual language research centers, fund individual researchers, and ensure that these developments are rapidly integrated into education and into the support of the other converging technologies.

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SOCIABLE TECHNOLOGIES: ENHANCING HUMAN PERFORMANCE WHEN THE COMPUTER IS NOT A TOOL BUT A COMPANION

Sherry Turkle, Massachusetts Institute of Technology

> *"Replacing human contact [with a machine] is an awful idea. But some people have no contact [with caregivers] at all. If the choice is going to a nursing home or staying at home with a robot, we think people will choose the robot."* Sebastian Thrun, Assistant Professor of Computer Science, Carnegie Mellon University
>
> *"AIBO [Sony's household entertainment robot] is better than a real dog. It won't do dangerous things, and it won't betray you. ...Also, it won't die suddenly and make you feel very sad.'"* A 32-year -old woman on the experience of playing with AIBO
>
> "*Well, the Furby is alive for a Furby. And you know, something this smart should have arms. It might want to pick up something or to hug me."* Ron, age six, answering the question, "Is the Furby alive?"

Artificial intelligence has historically aimed at creating objects that might improve human performance by offering people intellectual complements. In a first stage, these objects took the form of tools, instruments to enhance human reasoning, such as programs used for medical diagnosis. In a second stage, the boundary between the machine and the person became less marked. Artificial intelligence technology functioned more as a prosthetic, an extension of human mind. In recent years, even the image of a program as prosthetic does not capture the intimacy people have with computational technology. With "wearable" computing, the machine comes closer to the body, ultimately continuous with the body, and the human person is redefined as a cyborg. In recent years, there has been an increased emphasis on a fourth model of enhancing human performance through the use of computation: technologies that would improve people by offering new forms of social relationships. The emphasis in this line of research is less on how to make machines "really" intelligent (Turkle 1984, 1995) than on how to design artifacts that would cause people to experience them as having subjectivities that are worth engaging with.

The new kind of object can be thought of as a relational artifact or as a sociable technology. It presents itself as having affective states that are influenced by the object's interactions with human beings. Today's relational artifacts include children's playthings (such as Furbies, Tamagotchis, and My Real Baby dolls); digital dolls and robots that double as health monitoring systems for the elderly (Matsushita's forthcoming Tama, Carnegie Mellon University's Flo and Pearl); and pet robots aimed at the adult (Sony's AIBO, MIT's Cog and Kismet). These objects are harbingers of a new paradigm for computer-human interaction.

In the past, I have often described the computer as a Rorschach. When I used this metaphor I was trying to present the computer as a relatively neutral screen onto which people were able to project their thoughts and feelings, a mirror of mind and self. But today's relational artifacts make the Rorschach metaphor far less useful. The computational object is no longer affectively "neutral." Relational artifacts do

not so much invite projection as demand engagement. People are learning to interact with computers through conversation and gesture. People are learning that to relate successfully to a computer you do not have to know how it works but can take it "at interface value," that is, assess its emotional "state," much as you would if you were relating to another person. Through their experiences with virtual pets and digital dolls, which present themselves as loving and responsive to care, a generation of children is learning that some objects require emotional nurturing and some even promise it in return. Adults, too, are encountering technology that attempts to offer advice, care, and companionship in the guise of help-software-embedded wizards, intelligent agents, and household entertainment robots such as the AIBO "dog."

New Objects are Changing Our Minds

Winston Churchill once said, "We make our buildings and then they make us." We make our technologies, and they in turn shape us. Indeed, there is an unstated question that lies behind much of our historic preoccupation with the computer's capabilities. That question is not what can computers do or what will computers be like in the future, but instead, what will we be like? What kind of people are we becoming as we develop more and more intimate relationships with machines? The new technological genre of relational, sociable artifacts is changing the way we think. Relational artifacts are new elements in the categories people use for thinking about life, mind, consciousness, and relationship. These artifacts are well positioned to affect people's way of thinking about themselves, about identity, and about what makes people special, influencing how we understand such "human" qualities as emotion, love, and care. We will not be taking the adequate measure of these artifacts if we only consider what they do *for* us in an *instrumental* sense. We must explore what they do not just for us but to us as people, to our relationships, to the way our children develop, to the way we view our place in the world.

There has been a great deal of work on how to create relational artifacts and maximize their ability to evoke responses from people. Too little attention, however, has gone into understanding the human implications of this new computational paradigm, both in terms of how we relate to the world and in terms of how humans construct their sense of what it means to be human and alive. The language for assessing these human implications is enriched by several major traditions of thinking about the role of objects in human life.

Objects as Transitional to Relationship

Social scientists Claude Levi-Strauss (1963), Mary Douglas (1960), Donald Norman (1988), Mihaly Csikzentmihalyi (1981), and Eugene Rochberg-Halton (1981) have explored how objects carry ideas, serving as enablers of new individual and cultural meanings. In the psychoanalytic tradition Winnicott (1971) has discussed how objects mediate between the child's earliest bond with the mother, who the infant experiences as inseparable from the self, and the child's growing capacity to develop relationships with other people, who will be experienced as separate beings.

In the past, the power of objects to act in this transitional role has been tied to the ways in which they enabled the child to project meanings onto them. The doll or the teddy bear presented an unchanging and passive presence. Relational artifacts take a more active stance. With them, children's expectations that their dolls want to be

hugged, dressed, or lulled to sleep don't come from the child's projection of fantasy or desire onto inert playthings, but from such things as a digital doll's crying inconsolably or even saying, "Hug me!" "It's time for me to get dressed for school!" The psychology of the playroom turns from projection to social engagement, in which data from an active and unpredictable object of affection helps to shape the nature of the relationship. On the simplest level, when a robotic creature makes eye contact, follows your gaze, and gestures towards you, what you feel is the evolutionary button being pushed to respond to that creature as a sentient and even caring other.

Objects as Transitional to Theories of Life

The Swiss psychologist Jean Piaget addressed some of the many ways in which objects carry ideas (1960). For Piaget, interacting with objects affects how the child comes to think about space, time, the concept of number, and the concept of life. While for Winnicott and the object relations school of psychoanalysis, objects bring a world of people and relationships inside the self, for Piaget objects enable the child to construct categories in order to make sense of the outer world. Piaget, studying children in the context of non-computational objects, found that as children matured, they homed in on a definition of life that centered around "moving of one's own accord." First, everything that moved was taken to be alive, then only those things that moved without an outside push or pull. Gradually, children refined the notion of "moving of one's own accord" to mean the "life motions" of breathing and metabolism.

In the past two decades, I have followed how computational objects change the ways children engage with classic developmental questions such as thinking about the property of "aliveness." From the first generation of children who met computers and electronic toys and games (the children of the late 1970s and early 1980s), I found a disruption in this classical story. Whether or not children thought their computers were alive, they were sure that how the toys moved was not at the heart of the matter. Children's discussions about the computer's aliveness came to center on what the children perceived as the computer's psychological rather than physical properties (Turkle 1984). Did the computer know things on its own or did it have to be programmed? Did it have intentions, consciousness, feelings? Did it cheat? Did it know it was cheating? Faced with intelligent machines, children took a new world of objects and imposed a new world order. To put it too simply, motion gave way to emotion, and physics gave way to psychology as criteria for aliveness.

By the 1990s, that order had been strained to the breaking point. Children spoke about computers as just machines but then described them as sentient and intentional. They talked about biology, evolution. They said things like, "the robots are in control but not alive, would be alive if they had bodies, are alive because they have bodies, would be alive if they had feelings, are alive the way insects are alive but not the way people are alive; the simulated creatures are not alive because they are just in the computer, are alive until you turn off the computer, are not alive because nothing in the computer is real; the Sim creatures are not alive but almost-alive, they would be alive if they spoke, they would be alive if they traveled, they're not alive because they don't have bodies, they are alive because they can have babies and would be alive if they could get out of the game and onto America Online."

There was a striking heterogeneity of theory. Children cycled through different theories to far more fluid ways of thinking about life and reality, to the point that my daughter upon seeing a jellyfish in the Mediterranean said, "Look, Mommy, a jellyfish; it looks so realistic!" Likewise, visitors to Disney's Animal Kingdom in Orlando have complained that the biological animals that populated the theme park were not "realistic" compared to the animatronic creatures across the way at Disneyworld.

By the 1990s, children were playing with computational objects that demonstrated properties of evolution. In the presence of these objects, children's discussions of the aliveness question became more complex. Now, children talked about computers as "just machines" but described them as sentient and intentional as well. Faced with ever more sophisticated computational objects, children were in the position of theoretical tinkerers, "making do" with whatever materials were at hand, "making do" with whatever theory could be made to fit a prevailing circumstance (Turkle 1995).

Relational artifacts provide children with a new challenge for classification. As an example, consider the very simple relational artifact, the "Furby." The Furby is an owl-like interactive doll, activated by sensors and a pre-programmed computer chip, which engages and responds to their owners with sounds and movement. Children playing with Furbies are inspired to compare and contrast their understanding of how the Furby works to how they "work." In the process, the line between artifact and biology softens. Consider this response to the question, "Is the Furby alive?"

> Jen (age 9): I really like to take care of it. So, I guess it is alive, but it doesn't need to really eat, so it is as alive as you can be if you don't eat. A Furby is like an owl. But it is more alive than an owl because it knows more and you can talk to it. But it needs batteries so it is not an animal. It's not like an animal kind of alive.

Jen's response, like many others provoked by playing with Furbies, suggests that today's children are learning to distinguish between an "animal kind of alive" and a "Furby kind of alive." In my conversations with a wide range of people who have interacted with relational artifacts — from five year olds to educated adults — an emergent common denominator has been the increasingly frequent use of "sort of alive" as a way of dealing with the category confusion posed by relational artifacts. It is a category shared by the robots' designers, who have questions about the ways in which their objects are moving toward a kind of consciousness that might grant them a new moral status.

Human-Computer Interaction

The tendency for people to attribute personality, intelligence, and emotion to computational objects has been widely documented in the field of human-computer interaction (HCI) (Weizenbaum 1976; Nass, Moon, et al. 1997, Kiesler and Sproull 1997; Reeves and Nass 1999). In most HCI work, however, this "attribution effect" is considered in the context of trying to build "better" technology.

In *Computers are Social Actors: A Review of Current Research,* Clifford Nass, Youngme Moon, and their coauthors (1997) review a set of laboratory experiments in which "individuals engage in social behavior towards technologies even when

such behavior is entirely inconsistent with their beliefs about machines" (p. 138). Even when computer-based tasks contained only a few human-like characteristics, the authors found that subjects attributed personality traits and gender to computers and adjusted their responses to avoid hurting the machines' "feelings." The authors suggest that "when we are confronted with an entity that [behaves in human-like ways, such as using language and responding based on prior inputs] our brains' default response is to unconsciously treat the entity as human" (p. 158). From this, they suggest design criteria: technologies should be made more "likeable":

> … "liking" leads to various secondary consequences in interpersonal relationships (e.g., trust, sustained friendship, etc.), we suspect that it also leads to various consequences in human-computer interactions (e.g., increased likelihood of purchase, use, productivity, etc.) (p. 138).

Nass et al. prescribe "likeability" for computational design. Several researchers are pursuing this direction. At the MIT Media Lab, for example, Rosalind Picard's Affective Computing research group develops technologies that are programmed to assess their users'' emotional states and respond with emotional states of their own. This research has dual agendas. On the one hand, affective software is supposed to be compelling to users — "friendlier," easier to use. On the other hand, there is an increasing scientific commitment to the idea that objects need affect in order to be intelligent. As Rosalind Picard writes in *Affective Computing* (1997, x),

> I have come to the conclusion that if we want computers to be genuinely intelligent, to adapt to us, and to interact naturally with us, then they will need the ability to recognize and express emotions, to have emotions, and to have what has come to be called "emotional intelligence."

Similarly, at MIT's Artificial Intelligence Lab, Cynthia Breazeal has incorporated both the "attribution effect" and a sort of "emotional intelligence" in Kismet. Kismet is a disembodied robotic head with behavior and capabilities modeled on those of a pre-verbal infant (see, for example, Breazeal and Scassellati 2000). Like Cog, a humanoid robot torso in the same lab, Kismet learns through interaction with its environment, especially contact with human caretakers. Kismet uses facial expressions and vocal cues to engage caretakers in behaviors that satisfy its "drives" and its "emotional" needs. The robot "wants" to be happy, and people are motivated to help it achieve this goal. Its evocative design seems to help, Breazeal reports: "When people see Cog they tend to say, 'That's interesting.' But with Kismet they tend to say, 'It smiled at me!' or 'I made it happy!'" (Whynott 1999). I have seen similar reactions between children and simpler digital pets (both on the screen, such as neopets and in robotic form, such as Furbies and AIBOs).

When children play with Furbies, they want to know the objects' "state," not to get something "right," but to make the Furbies happy. Children want to understand Furby language, not to "win" in a game over the Furbies, but to have a feeling of mutual recognition. When I asked her if her Furby was alive, Katherine, age five, answered in a way that typifies this response:

> "Is it alive? Well, I love it. It's more alive than a Tamagotchi because it sleeps with me. It likes to sleep with me."

Children do not ask how the Furbies "work" in terms of underlying process; they take the affectively charged toys "at interface value."

With the advent of relational artifacts and their uses of emotion, we are in a different world from the old AI debates of the 1960s to 1980s, in which researchers argued about whether machines could be "really" intelligent. The old debate was essentialist; these new objects allow researchers and their public to sidestep such arguments about what is inherent in the computer. Instead, they focus attention on what the objects evoke in us. When we are asked to care for an object (the robot Kismet or the plaything Furby), and when the cared-for object thrives and offers us its attention and concern, we experience that object as intelligent. Beyond this, we feel a connection to it. So the issue here is not whether objects "really" have emotions, but what is happening when relational artifacts evoke emotional responses in the users.

People's relationships with relational artifacts have implications for technological design (i.e., how to make the objects better, more compelling), and they have implications that are the focus of this research: they complicate people's ways of thinking about themselves, as individuals, as learners and in relationships, and within communities. To augment human potential, any discussion of how to make "better" relational artifacts must be in terms of how they can best enhance people in their human purposes. It cannot be discussed in terms of any absolute notions defined solely in terms of the objects.

The questions raised by relational artifacts speak to people's longstanding fears and hopes about technology, and to the question of what is special about being human, what is the nature of "personhood." In the case of relational technology, there is a need for examination of these questions, beginning with how these objects are experienced in the everyday lives of the individuals and groups who are closest to them.

Human Performance

When people learn that AIBO, the Sony robot dog, is being introduced into nursing homes as companions to the elderly, the first question asked is usually, "Does it work?" By this the person means, "Are the old people happier when they have a robot pet? Are they easier to take care of?" My vision of the future is that we are going to have increasingly intimate relationships with sociable technologies, and we are going to need to ask increasingly complex questions about the kinds of relationships we form with them. The gold standard cannot be whether these objects keep babies and/or the elderly "amused" or "quiet" or "easier to care for." Human performance needs to be defined in a much more complex way, beginning with a set of new questions that take the new genre of objects seriously. Taking them seriously means addressing them as new social interlocutors that will bring together biology, information science, and nanoscience. Human performance needs to take into account the way we feel about ourselves as people, in our relationships and in our social groups. From this point of view, the question for the future is not going to be whether children love their robots more than their parents, but what loving itself comes to mean. From this perspective on human enhancement, some of the questions are

- How are children adapting ideas about aliveness, intentionality, and emotion to accommodate relational artifacts?
- How are designers and early adopters adapting ideas about personhood, intentionality, and relationship to accommodate relational artifacts? How do these artifacts influence the way people think about human minds?
- How are people thinking about the ethical issues raised by relational artifacts? Is a moral code for the treatment of this new type of artifacts being developed?
- How are people using relational artifacts to address needs traditionally met by other humans and animal pets, such as companionship and nurturing?

A Vision Statement

Computational objects are "evocative objects." They raise new questions and provoke new discourse about the nature of mind, about what it means to be alive, about what is special about being a person, about free will and intentionality. Computation brings philosophy into everyday life. Objects as simple as computer toys and games raise such questions as "What is intelligence? What does it mean to be alive? Or to die? What is the nature of the self? What is special about being a person?" In the next 10 to 20 years, research that will marry biology, information science, cognitive science, and nanoscience is going to produce increasingly sophisticated relational, sociable artifacts that will have the potential to profoundly influence how people think about learning, human development, intelligence, and relationships.

- As research on relational and sociable technology progresses, there will be parallel investigations of how these objects affect the people who use them, how they influence psychological development, human relationships, and additionally, how they enter into people's thinking about themselves, including about such questions as the nature of intention, the self, and the soul.
- The development of sociable technologies will require a renaissance in the sciences that study human development and personality. There will be an increasing virtuous cycle of research to understand human personality and to create person-enhancing machines. Indeed, the notion of personable machines will come to mean person-enhancing machines.
- In the past, it has been argued that technology dehumanized life, but as we become committed to person-enhancing objects, this argument will need to be revisited. Making technology personable will entail learning about ourselves. In order to make technology enhance humans, we will humanize technology.
- Historically, when technology has been designed without human fulfillment in mind, but purely in terms of the instrumental capabilities of the machine, there has been a great deal of resistance to technology. This resistance needs to be taken seriously, because it points to the ways in which people associate technology with human loss. The development of sociable technology will require that there be a flourishing of research that takes resistance to technology as a symptom of something important that needs to be studied

rather than a problem that needs to be overcome. An understanding of human psychology is essential for the development of sociable technologies. This latter will proceed with vigilance and with the participation of humanists and scientists. Sociable technology will enhance human emotional as well as cognitive performance, not only giving us more satisfactory relationships with our machines but also potentially vitalizing our relationships with each other, because in order to build better sociable objects we will have learned more about what makes us social with each other.

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VISIONARY PROJECTS

SOCIO-TECH…THE PREDICTIVE SCIENCE OF SOCIETAL BEHAVIOR

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Socio-tech is the predictive — not descriptive — science of the behavior of societies. It is the convergence of information from the life sciences, the behavioral sciences (including psychology and the study of cognition), and the social sciences. Its data gathering and analysis approaches come from these fields and are significantly augmented by new tools from fields such as nanotechnology, engineering, and the information sciences. Agent-based simulations, models incorporating genetic algorithms, evolutionary computing techniques, and brain-machine interfaces provide new ways to gather data and to analyze the results.

Why Do We Care?

Most immediately, socio-tech can help us win the war on terrorism. It can help us to understand the motivations of the terrorists and so eliminate them. It also can help us to manage ourselves, to orchestrate our own country's response to a potential or real attack. In the longer term, as a predictive science, socio-tech can help us identify possible drivers for a wide range of socially disruptive events and allow us to put mitigating or preventative strategies in place before the fact.

What Is New?

The multiple drivers of human behavior have long been known. What have been missing are the theoretical paradigm and associated tools to integrate what we know about these drivers into an overarching understanding of human activity.

Currently, most of the data related to understanding human behavior has remained field-specific. The life sciences focus on the biological impacts of humans

[1] Sandia National Laboratories is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy under Contract DE-AC04-94AL85000.

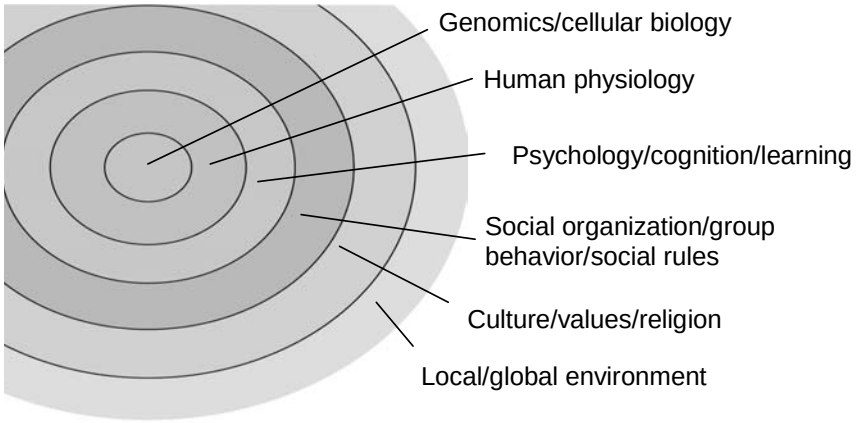

Figure B.11. Integrated studies of human behavior: Socio-tech.

functioning in physical spaces. The social sciences focus on the organizing principles of groups (rule of law, social hierarchies) and the different values groups place on behaviors (e.g., through culture or religion). The behavioral sciences are concerned with the functioning of the brain and the impact of individual experience on decision-making. The tools of science, engineering, and the information and computational sciences generally are not well integrated into these fields. C.P. Snow's 1959 Rede lecture captured this divide between the sciences on one hand and the arts and humanities on the other by the term "the two cultures."

There is little dialogue among practitioners from these different areas. They are separated by barriers of jargon, by conceptual frameworks that are difficult to translate from one field to another, and by traditional institutional compartmentalization of intellectual disciplines. Efforts such as Lewis Mumford's *Techniques and Human Development* (1989) to socially contextualize technology or E.O. Wilson's more recent and ambitious *Concilience* (1999) are the exceptions rather than the rule. We thus have no true study of human behavior, for there is no field or discipline with the interest or the tools to integrate data from these different fields. The challenge before us is to devise a way to understand data and information from each field in the context of all others. If genomics can be practiced with an awareness of human physiology, behavior, values, and environment, and, conversely, if information from genomics can be incorporated in a meaningful way into studies in these other fields, we will have made a significant leap in our understanding of human behavior (Figure B.11).

Why Now?

The time is ripe to begin such integration — to use the tremendous computing power we now have to integrate data across these fields to create new models and hence new understanding of the behavior of individuals. The ultimate goal is acquiring the ability to predict the behavior of an individual and, by extension, of groups. Recent advances in brain imaging, neuropsychology, and other sciences of the brain have significantly contributed to our knowledge of brain functioning. Genomics, molecular biology, and contributions from other areas in the life sciences

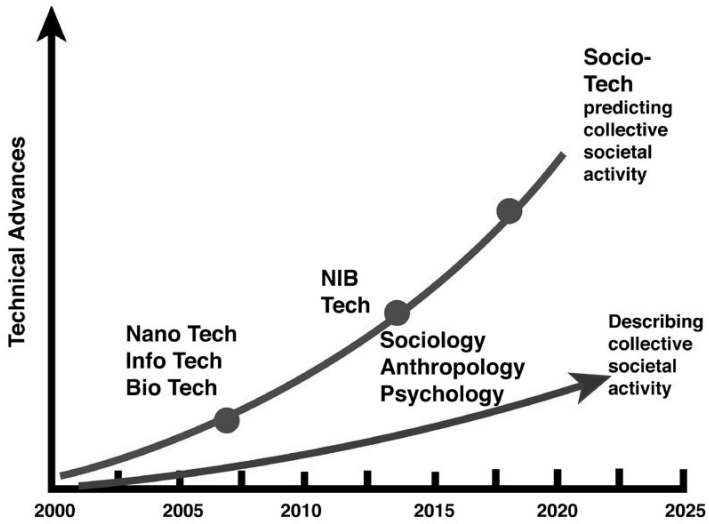

Figure B.12. Socio-tech: A qualitatively new science.

have greatly advanced our knowledge of the human body, its genetic core, and its response to various environmental stimuli. The increasing body of knowledge in the social sciences, combined with the tremendous computing (analysis) power available at affordable prices and new tools for communication and expression, have given us new ways of looking at social relationships such as social network theory, and new ways of understanding different ways of life. Incorporating these advances in a wide range of fields of study into overarching and integrating conceptual models should give us significant insights into human behavior.

Figure B.12 shows two possible trajectories for the development of knowledge. The upper trajectory combines the "two cultures," using technology to leverage the behavioral and social sciences and leads to a predictive science of behavior. The lower trajectory illustrates improvements in the behavioral and social sciences, with little incorporation of theory and tools from science and technology. It leads to greater descriptive but no predictive capabilities.

Socio-tech — the accumulation, manipulation, and integration of data from the life, social, and behavioral sciences, using tools and approaches provided by science and technology — will raise our ability to predict behaviors. It will allow us to interdict undesirable behaviors before they cause significant harm to others and to support and encourage behaviors leading to greater social goods.

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BREAKING THE LIMITS ON DESIGN COMPLEXITY

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As we contemplate microelectromechanical systems (MEMS) and nanotechnologies (nano), we must study the history of the design of circuits and software, especially software that is supposed to have cognitive function, or artificial intelligence (AI). Having been working in the field of AI for 25 years, I can say with some authority that nanotechnology will not solve the AI problem. In fact, the repeated failures of AI artifacts to live up to claims made by their proponents can shed light on human expectations of nano and on the capacity of human teams to design complex objects.

We think that in order to design products "of biological complexity" that could make use of the fantastic fabrication abilities of new nano and MEMS factories, we must first liberate design by discovering and exploiting the principles of automatic self-organization that are seen in nature. A brain has 10^{11} connections. Chemistry often works with 10^{23} molecules. Advanced software is the most complex (and profitable) of all of human artifacts, yet each application only comprises between 10 million and 100 million lines of code, or a maximum of around 10^8 moving parts. Suppose an animal brain, rather than requiring the specifying over time of the bonds for every molecule, ONLY required the equivalent of 10^{10} uniquely programmed parts. Why can't we engineer that?

In circuits, achieving even a function as lowly as the "bit" of memory creates a means to replication. Now we have 32 million bits on a single chip, and that is an achievement. Building blocks that can be replicated via manufacturing in hardware make things like memory chips and CPUs faster and more capable. This replication capacity and speedup of hardware enables Moore's law, a doubling of computer power, and even disk space, every 18 months. However, this periodic doubling of computer power has not led to equivalent doubling of human capacity to manufacture significantly more complex software. Moore's law does not solve the problem of engineering 10 billion lines of code!

The simple reason we haven't witnessed Moore's law operate for software is that 32 million copies of the same line of code is just one more line of code — the DO loop. Thus today's supercomputers run the same sized programs as the supercomputers of the 1970s, which are the desktops of today. The applications can use lots of floating point multiplication, but the complexity of the tasks hasn't grown beyond word processing, spreadsheets, and animations. Faster and faster computers seem to encourage software companies to write less and less efficient code for the same essential functionality — Windows is just DOS with wallpaper.

We've learned this hard lesson from the field of software — which isn't even constrained by material cost or by physical reality: *there are limits on the complexity of achievable design*. This is true even when throwing larger and larger teams of humans at a problem, even with the best groupware CAD software, even with bigger computers. Therefore, assumptions that new fabrication methodologies will lead to a breakthrough in design complexity ought to be taken with a grain of salt.

Yet many nano pundits expect that smaller-scale manufacturing, rather than leading to homogenous materials competitive with wood and plastic, will automatically lead to artificial objects of extraordinary complexity and near life-like

capacity. They seem to ignore the technical challenges of understanding and modeling cognition, plugging portals into our brains, and programming Utility Fogs of nanobots that are intelligent enough to swarm and perform coordinated missions. The reality is that making life-sized artifacts out of molecules may require the arranging of 10^{30} parts.

AI is stalled because it is starved of the much more complex blueprints than anyone has any clue how to build. Software engineering seems to have reached a complexity limit well below what computers can actually execute. Despite new programming languages and various movements to revolutionize the field, the size of programs today is about the same as it has been for 40 years: 10-100 million lines of code. Old code finally collapses under the cost of its own maintenance.

The high-level languages, object-oriented programming systems, and computer-assisted software engineering (CASE) breakthroughs have all seemed promising, yet each new breakthrough devolves back into the same old thing in new clothes: the Fortran compiler plus vast scientific libraries. The power of each new programming tool, be it PL/1, Turbo Pascal, Visual Basic, Perl, or Java, is located in the bundled collections of subroutine libraries, which eventually grow to surpass our merely human cognitive ability to remember or even look them up in burgeoning encyclopedias.

The problem illustrated here is still Brooks' Mythical Man Month: We can't get bigger and better software systems by putting more humans on the job. The best original software, whether DOS, Lotus 123, or Wordstar, have been written by one or two good programmers; large teams extend, integrate, copy, and maintain, but they do not create. The more programmers on a task, the more bugs they create for each other.

The opportunity available today is that the way out of this tarpit, the path to achieving both software and nano devices of biological complexity with tens of billions of moving parts, is very clear: it is through increasing our scientific understanding of the processes by which biologically complex objects arose. As we understand these processes, we will be able to replicate them in software and electronics. The principles of automatic design and of self-organizing systems are a grand challenge to unravel. Fortunately, remarkable progress has been shown since the computer has been available to refine the theory of evolution. Software is being used to model life itself, which has been best defined as that "chemical reaction, far from equilibrium, which dissipates energy and locally reverses entropy."

Much as logic was unconstrained philosophy before computer automation, and as psychological and linguistic theories that could not be computerized were outgunned by formalizable models, theories on the origin of life, its intrinsic metabolic and gene regulation processes, and the mechanisms underlying major transitions in evolution, are being sharpened and refuted through formalization and detailed computer simulation.

Beyond the basic idea of a genetic algorithm, the variety of studies on artificial life, the mathematical and computational bases for understanding learning, growth, and evolution, are rapidly expanding our knowledge and our know-how.

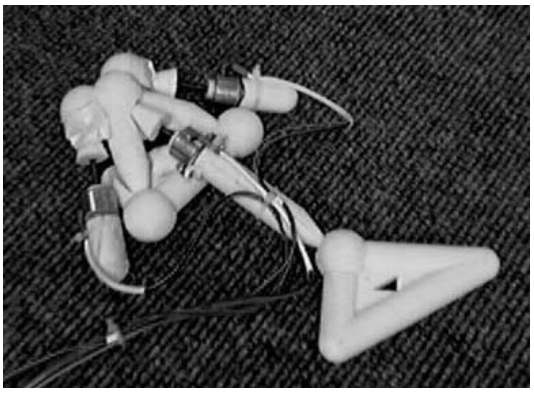

Figure B.13. Semi- and fully automatic design can help design complex systems like robot hardware and software.

My laboratory, which studies machine learning and evolutionary computation, has focused on how semi- and fully-automatic design can help design complex systems like robot hardware and software. We have used a collection of methods called "co-evolution," in which the idea is to create a sustained "arms-race" amongst or between populations of simple learning systems in order to achieve automatic design of various structures such as sorting nets, cellular automata rules, game players, and robot bodies and brains (Fig. B.13).

The field of evolutionary design, which aims at the creation of artifacts with less human engineering involvement, is in full force, documented by the books edited by Peter Bentley, as well as a NASA-sponsored annual conference on evolutionary hardware. Evolutionary robotics is a related field that started with Karl Sims' virtual robots and has grown significantly in the last five years.

So far, few artificial evolutionary processes have produced software or systems beyond those that can be designed by teams of humans. But they are competitive, and they are much cheaper than human designs. More importantly, thus far, they have not hit a barrier to complexity as seen in software engineering. Automatic design converts surplus computer time into complex design, and this will be aided by Moore's law. As inexpensive one-of-a-kind fabrication becomes possible, mass manufacture will no longer be necessary to amortize the fixed costs of engineering design, and automatic design will become necessary to generate complex designs with low cost. Success in this field holds keys to surpassing today's limits on complexity.

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ENHANCING PERSONAL AREA SENSORY AND SOCIAL COMMUNICATION THROUGH CONVERGING TECHNOLOGIES

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The next decade will see great strides in personal wearable technologies that enhance people's ability to sense their environment. This sensing will focus on at least two different areas:

a) *social sensing*, in which we may augment our ability to be aware of people in our immediate vicinity with whom we may wish to connect (or possibly avoid!)

b) *environmental sensing*, in which we may augment our ability to sense aspects of our environment (for example, the quality of the air we are breathing) that may be hazardous to us but that our normal senses cannot detect

Social Sensing

Few would question the remarkable extent to which the two pillars of modern day business communication — cell phones and email — enable us to effortlessly stay in touch with people on the other side of the planet. The paradox lurking behind this revolution is that these same technologies are steadily eroding the time and attention we devote to communicating with people in our immediate vicinity. The cost to the sender of sending an email or placing a cellular call is rapidly approaching zero. Unchecked, the cost to the recipient may rapidly become unmanageable, not in terms of financial cost, but rather in terms of demands on our time and attention. Witness the now common scene in airports and other public spaces — hundreds of people milling around in what appears to be animated conversation; on closer inspection, it turns out that they are not with each other, but rather with people connected to them via the near-invisible ear bud microphones they are wearing. Similarly, it is common to observe business colleagues in offices sitting just a few feet away from each other engaged in passionate debate. But the debate is often not verbal; rather, the only sound is the click-clack of keyboards as email flies back and forth. In desperation, some companies have resorted to the draconian measure if banning emails on certain days of the week ("email-free Fridays") or certain core hours of the day as the only way to pry their employees away from the email inboxes to engage in face-to-face dialog.

Why is it that so many people seem to find communication through email or cell phone more compelling than face-to-face dialog? Many value the fact that email permits asynchronous communication, enabling the recipient to respond only when it is convenient for them. Email also enables people to reinvent their personalities in ways that would be difficult or impossible for them socially. Cell phone technology

has conquered geographical separation — anytime, anywhere communication. Rather than pursuing a chance encounter with the stranger standing next to me, it seems easier to talk to someone I know over a cell phone.

In contrast, technology has done little or nothing to enhance face-to-face communication. As we move from the current era of computing (so-called "personal" computers) to the next era (described variously as ambient intelligence or ubiquitous computing), help for social dialog will arrive in the form of next-generation personal information managers (PIMs) connected via wireless Personal Area Networks (PANs). PANs operate over a distance of just a few feet, connecting an individual to just those people within their immediate vicinity — their dinner companions, for example. First-generation PAN devices will be based on Bluetooth wireless technology.

Next generation PIMs arriving on the market over the next 24-36 months will store their owner's personal profile that will contain whatever information the owner may wish to share with others in their immediate vicinity. The information a user may wish to exchange in this way will obviously depend on the social context that the user is in at any given moment. In contrast to today's PIMs (where a lot of fumbling around will eventually result in a digital business card being exchanged between two devices), rich personal information will flow automatically and transparently between devices. It is quite likely that these PIMs will evolve to look nothing like today's devices. They may be incorporated into a pair of eyeglasses, or even in the clothes that we wear.

Widespread use of such devices will, of course, require that issues of personal privacy be resolved. However, peer-to-peer ad hoc networks of this type are inherently more respectful of individual privacy than client server systems. Users of PAN devices can specify either the exact names or the profiles of the people with whom they want their devices to communicate. They may also choose to have any information about themselves that is sent to another device time-expire after a few hours. This seems relatively benign compared to the information that can be collected about us (usually without our knowledge or consent) every time we browse the Web.

Many of us attend conferences every year for the purpose of professional networking. At any given conference of a hundred people or more, it is likely that there are a handful of potentially life-transforming encounters that could happen within the group. But such encounters are reliant on a chain of chance meetings that likely will not happen, due to the inefficiencies of the social network. Personal Area Network devices could dramatically improve our ability to identify the people in a crowd with whom we may wish to talk. Of course, we will want sophisticated software agents acting on our behalf to match our interests with the profiles of the people standing around us. We could even imagine a peer-to-peer Ebay in which my profile indicates that I am in the market to buy a certain type of car and I am alerted if anyone around me is trying to sell such a car. In Japan, it is already possible to buy a clear plastic key chain device that can be programmed to glow brightly when I encounter someone at a party whose interests are similar to mine. A high tech icebreaker!

The most profound technologies are the ones that "disappear" with use. Personal Area Network devices may enable nothing fundamentally new — they may just simplify what we already do

Environmental Sensing

We rely heavily on our natural senses (touch, sight, sound, smell) to keep us out of danger. Recent events are likely to have a lasting impact on the public's awareness that there are an increasing number of hazards that our biological senses do not help us avoid. This desire for enhanced personal area environmental awareness is not simply a function of the anthrax scare. We will increasingly want to know more about the safety of air we breathe, the water that we drink, and the things we touch. This must be accomplished without bulky instrumentation and provide realtime feedback. I expect considerable commercial effort to be devoted towards transparent technology for personal environmental sensing. This may take the form of clothing that contains chemicals that change color in the presence of certain biohazards. Equally, we can expect a new generation of nano-sensors, custom-built to detect the presence of specific molecules, to be built into our clothing. Wearable technology presents great design challenges given the need to fold and wash the fabrics, maintain wearability, fashion, and light weight. For this reason, we should expect development in this arena to focus on chemical and nano-scale sensing. We have long expected our clothing to protect us from our surroundings — whether it be from the cold, UV radiation, or industrial hazards. Designing clothes that provide protection (through awareness) from other environmental hazards is a logical extension of the function of clothing to date.

THE CONSEQUENCES OF FULLY UNDERSTANDING THE BRAIN

Warren Robinett

We start with questions:

- How does memory work?
- How does learning work?
- How does recognition work?
- What is knowledge?
- What is language?
- How does emotion work?
- What is thought?

In short, how does the brain work?

We have nothing better than vague, approximate answers to any of these questions at the present time, but we have good reason to believe that they all have detailed, specific, scientific answers, and that we are capable of discovering and understanding them.

We want the questions answered in full detail — at the molecular level, at the protein level, at the cellular level, and at the whole-organism level. A complete answer must necessarily include an understanding of the developmental processes

that build the brain and body. A complete answer amounts to a wiring diagram of the brain, with a detailed functional understanding of how the components work at every level, from whole brain down to ion channels in cell walls. *These are questions of cognitive science, but to get detailed, satisfying, hard answers, we need the tools of nanotechnology, biochemistry, and information technology.*

How important would it be if we did achieve full understanding of the brain? What could we do that we can't do now? How would it make our lives better? Unfortunately, scientific advances don't always improve the quality of life. Nevertheless, let's look at some possibilities opened up by a full understanding of how the brain works.

New Capabilities Enabled by Full Understanding of the Brain

We understand the input systems to the brain — the sensory systems — better than the rest of the brain at this time. Therefore, we start with ways of fooling the senses by means of electronic media, which can be done now, using our present understanding of the senses.

Virtual Presence

The telephone, a familiar tool for all of us, enables auditory-only virtual presence. In effect, your ears and mouth are projected to a distant location (where someone else's ears and mouth are), and you have a conversation *as if you were both in the same place.* Visual and haptic (touch) telepresence are harder to do, but nevertheless it will soon be possible to electronically project oneself to other physical locations and have the perceptions you would have if you were actually there — visually, haptically, and aurally, with near-perfect fidelity.

Tasks that could be accomplished with virtual presence include the following:

- meeting with one or more other people; this will be an alternative to business travel but will take the time of a telephone call rather than the time of a cross-country airplane flight
- interacting with physical objects in a distant location, perhaps a hazardous environment such as a nuclear power plant interior or battlefield, where actual human presence is impossible or undesirable
- interacting with objects in microscopic environments, such as in the interior of a human body (I have worked on a prototype system for doing this, the NanoManipulator; see http://www.WarrenRobinett.com/nano/)

Better Senses

Non-invasive, removable sensory enhancements (eyeglasses and contact lenses) are used now and are a useful first step. But why not go the second step and surgically correct the eyeball? Even better, replace the eyeball. As with artificial hips and artificial hearts, people are happy to get a new, better component; artificial sensory organs will follow. We can look at binoculars, night-vision goggles, and Geiger counters (all currently external to the body) to get an idea of what is possible: better resolution, better sensitivity, and the ability to see phenomena (such as radioactivity) that are normally imperceptible to humans. Electronic technology can be expected to provide artificial sensory organs that are small, lightweight, and self-powered. An understanding of the sensory systems and neural channels will enable,

for example, hooking up the new high-resolution electronic eyeball to the optic nerve. By the time we have a full understanding of all human sensory systems, it is likely we will have a means of performing the necessary microsurgery to link electronic signals to nerves.

Better Memory

What is the storage mechanism for human memory? What is its architecture? What is the data structure for human memory? Where are the bits? What is the capacity of the human memory system in gigabytes (or petabytes)? Once we have answers to questions such as these, we can design additional memory units that are compatible with the architecture of human memory. A detailed understanding of how human memory works, where the bits are stored, and how it is wired will enable capacity to be increased, just as you now plug additional memory cards into your PC. For installation, a means of doing microsurgery is required, as discussed above. If your brain comes with 20 petabytes factory-installed, wouldn't 200 petabytes be better?

Another way of thinking about technologically-enhanced memory is to imagine that for your entire life you have worn a pair of eyeglasses with built-in, lightweight, high-resolution video cameras which have continuously transmitted to a tape library somewhere, so that every hour of everything you have ever seen (or heard) is recorded on one of the tapes. The one-hour tapes (10,000 or so for every year of your life) are arranged chronologically on shelves. So your fuzzy, vague memory of past events is enhanced with the ability to replay the tape for any hour and date you choose. Your native memory is augmented by the ability to reexperience a recorded past. Assuming nanotechnology-based memory densities in a few decades (1 bit per 300 nm^3), a lifetime (3×10^9 seconds) of video (10^9 bits/second) fits into 1 cubic centimeter. Thus, someday you may carry with you a lifetime of perfect, unfading memories.

Better Imagination

One purpose of imagination is to be able to predict what will happen or what might happen in certain situations in order to make decisions about what to do. But human imagination is very limited in the complexity it can handle. This inside-the-head ability to simulate the future has served us very well up to now, but we now have computer-based simulation tools that far outstrip the brain's ability to predict what can happen (at least in certain well-defined situations). Consider learning how to handle engine flameouts in a flight simulator: you can't do this with unaugmented human imagination. Consider being able to predict tomorrow's weather based on data from a continent-wide network of sensors and a weather simulation program. This is far beyond the amount of data and detail that human imagination can handle. Yet it is still the same kind of use of imagination with which we are familiar: predicting what might happen in certain circumstances. Thus, our native imagination may be augmented by the ability to experience a simulated future. At present, you can dissociate yourself from the flight simulator — you can get out. In future decades, with enormous computing power available in cubic micron-sized packages, we may find personal simulation capability built-in, along with memory enhancement, and improved sensory organs.

Now the Really Crazy Ones

Download Yourself into New Hardware

Imagine that the brain is fully understood, and therefore the mechanisms and data structures for knowledge, personality, character traits, habits, and so on are known. Imagine further that, for an individual, the data describing that person's knowledge, personality, and so forth, could be extracted from his brain. In that case, his mind could be "run" on different hardware, just as old video games are today run in emulation on faster processors. This, of course, raises lots of questions. What is it that makes you *you*? (Is it more than your knowledge and personality?) Is having the traditional body necessary to being human? Nevertheless, if you accept the above premises, *it could be done*. Having made the leap to new hardware for yourself, many staggering options open up:

- No death. You back yourself up. You get new hardware as needed.
- Turn up the clock speed. Goodbye, millisecond-speed neurons; hello, nanosecond-speed electronics.
- Choose space-friendly hardware. Goodbye, Earth; hello, galaxy.

Instant Learning

If the structure of knowledge were fully understood, and if we controlled the "hardware and software environment" of the mind, then presumably we would understand how new knowledge gets integrated with old knowledge. The quaint old-fashioned techniques of "books" and "school" would be reenacted sometimes for fun, but the efficient way would be to just get the knowledge file and run the integrate procedure. Get a Ph.D. in Mathematics with "one click."

Hive Mind

If we can easily exchange large chunks of knowledge and are connected by high-bandwidth communication paths, the function and purpose served by individuals becomes unclear. Individuals have served to keep the gene pool stirred up and healthy via sexual reproduction, but this data-handling process would no longer necessarily be linked to individuals. With knowledge no longer encapsulated in individuals, the distinction between individuals and the entirety of humanity would blur. Think Vulcan mind-meld. We would perhaps become more of a hive mind — an enormous, single, intelligent entity.

Speed-of-Light Travel

If a mind is data that runs on a processor (and its sensors and actuators), then that data — that mind — can travel at the speed of light as bits in a communication path. Thus, Mars is less than an hour away at light speed. (We needed a rocket to get the first receiver there.) You could go there, have experiences (in a body you reserved), and then bring the experience-data back with you on return.

Self-Directed Evolution

If mind is program and data, and we control the hardware and the software, then we can make changes as we see fit. What will human-like intelligence evolve into if it is freed from the limits of the human meat-machine, and humans can change and improve their own hardware? It's hard to say. The changes would perhaps be goal-

directed, but what goals would be chosen for self-directed evolution? What does a human become when freed from pain, hunger, lust, and pride? (If we knew the answer to this, we might be able to guess why we haven't detected any sign of other intelligences in the 100 billion stars of our galaxy!)

USER-INTERFACE OLYMPICS: USING COMPETITION TO DRIVE INNOVATION

Warren Robinett

Has bicycle racing improved bicycles? Yes, it has. We humans like to win, and like Lance Armstrong pedaling through the Alps in the Tour de France, we demand the best tools that can be made. The competition, the prestige of being the world champion, the passion to win, publicity for the chosen tools of the winners — these forces squeeze the imaginations of bicycle engineers and the bank accounts of bicycle manufacturers to produce a stream of innovations: lighter and higher-strength materials, more efficient gearing, easier and more reliable gear-shifting, aerodynamic improvements such as farings and encased wheels... the list goes on and on.

Competition spawns rapid improvements. Sounds a bit like evolution, doesn't it? *Lack of competition* can lead to long periods of quiescence, where nothing much changes. (Did you know the QWERTY keyboard was designed 100 years ago?)

This principle that *competition spawns improvement* could be applied to drive innovations in user-interface design. We call the proposed competition the *User-Interface Olympics*. Here is a sketch of how it might work:

- It would be an annual competition sponsored by a prestigious organization — let's say, the U.S. National Science Foundation.
- The winners would get prestige and possibly prize money (like the Nobel Prize, Pulitzer Prize, Emmies, Academy Awards, Oscars, and so on).
- The competition would be composed of a certain number of events, analogous to Olympic events. Individual contestants, or teams of contestants, compete for the championship in each event. User-interface events would be such things as
  - a timed competition to enter English text into a computer as fast as possible. (Surely someone can do better than the QWERTY keyboard!)
  - a timed competition to select a specified series of items from lists. (Can we improve on the 40-year-old mouse?)
- Contestants would provide their own tools. This is analogous to the equipment used by athletes (special shoes, javelin, ice skates). However, for the User-Interface Olympics, the tools are the hardware and software used by each competitor.
- Since the goal is to stimulate innovation, contestants would have to fully disclose the working of their tools. A great new idea would get you one gold

medal, not ten in a row. This is similar to the patent system, in which rewards during a limited period are bartered for disclosure and dissemination of ideas.

- An administrative authority would be needed, analogous in the Olympic Committee and its subordinate committees, to precisely define the rules for each event, for qualifying for events, and many other related matters. This Rules Committee would monitor the various events and make adjustments in the rules as needed.
- We would expect the rules of each event to co-evolve with the competitors and their tools. For example, the rule against goal tending in basketball was instituted in response to evolving player capabilities; in the 100-meter dash, precise rules for false starts must be continually monitored for effectiveness. Winning within the existing rules is not cheating, but some strategies that players may discover might not be really fair or might circumvent the intent of the competition. Of course, some competitors do cheat, and the rules must set reasonable penalties for each type of infraction. The Rules Committee would therefore have to evolve the rules of each event to keep the competition healthy.
- New events would be added from time to time.

These contests would be similar to multiplayer video games. The contestants would manipulate user-input devices such as the mouse, keyboard, joystick, and other input devices that might be invented. The usual classes of display devices (visual, aural, and haptic) would be available to the contestants, with innovations encouraged in this area, too. Most malleable, and therefore probably most fertile for spawning innovations, would be the software that defined the interaction techniques through which the contestant performed actions during the contest.

If we set things up right, perhaps we could tap some of the enormous energy that the youth of the nation currently pours into playing video games.

The rules for each contest, which would be published in advance, would be enforced by a computer program. Ideally, this referee program could handle all situations that come up in a contest; whether this actually worked, or whether a human referee would be needed, would have to determined in real contests. Making the referee completely automated would offer several advantages. Contests could be staged without hiring anyone. Computer referees would be, and would be perceived to be, unbiased. Early qualifying rounds could be held using the Internet, thus encouraging many contestants to participate. Figure B.14 shows a system diagram.

If this idea is to be attempted, it is critical to start with a well-chosen set of events. (Imagine that the Olympics had tried to start with synchronized swimming and sheep shearing!) A small, well-justified set of events might be best initially, just to keep it simple and try out the idea. One way to identify potential events for the UI Olympics is to look at input devices that currently are widely used:

- computer keyboard — suggests a text-entry event
- computer mouse — suggests an event based on selecting among alternatives
- joystick, car steering wheel — suggest one or more events about navigating through a 2-D or 3-D space

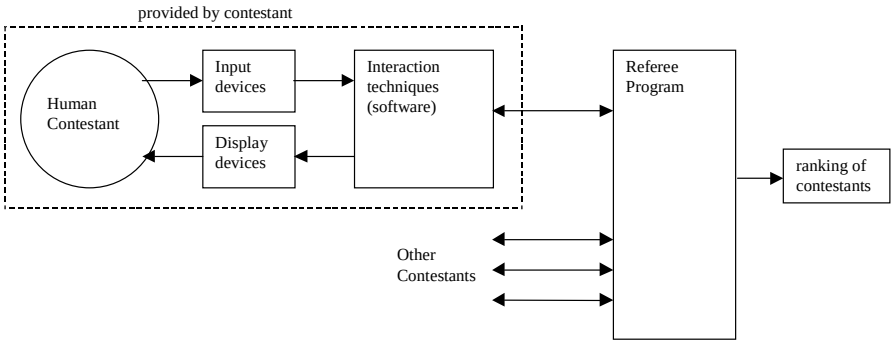

Figure B.14. System Diagram for a contest in the User-Interface Olympics, mediated by an automated referee program, with several contestants participating. The contestants provide their own hardware and software.

The real Olympics has events based both on raw power, speed, and stamina (weight lifting, races, and the marathon) and also events based on more complex skills (skiing, badminton, baseball). Similarly, the User-Interface Olympics could complement its events based on low-level skills (text entry, navigation) with some events requiring higher-level thinking. There are many kinds of "high-level thinking," of course. One class of well-developed intellectual contests is the mathematical competition. There are a number of well-known competitions or tests we can consider as examples: the MathCounts competitions run among middle schools and high schools; the Putnam Mathematical Competition run for undergraduates, and the math portion of the Scholastic Aptitude Test (or SAT, the college entrance test). Another similar competition is the annual student programming contest sponsored by the Association for Computing Machinery. One or more events based on solving well-defined categories of complex problems, using tools chosen by the contestant, would be desirable.

Strategy board games, such as chess and go, are another class of contests requiring complex skills. The rules for these games have already evolved to support interesting, healthy competitions and cultures. To focus on chess for a moment, by making chess an event in the User-Interface Olympics, we have an opportunity to reframe the false dichotomy between a human chess player and a chess-playing computer — we introduce a third possibility, a human contestant combined with her chess-analysis software. I personally believe that the combination of a good chess player, a good chess program, and a good user interface to integrate the two could probably beat both Deep Blue and Garry Kasparov. At any rate, this is a well-defined and testable hypothesis.

Therefore, the following events are proposed for the initial User-Interface Olympics:

- Text-entry speed competition
- Selection-among-alternatives race
- Navigation challenge: a race through a series of waypoints along a complex racecourse

- Timed math problems from the SAT (or equivalent problems)
- Timed chess matches

Each of these events would need precisely-formulated rules.

The strategy needed to achieve this vision of a thriving, well-known, self-perpetuating User-Interface Olympics that effectively drives innovation in user interface hardware and software is this:

- Fund the prizes for the first few years — let's say $100,000 for each of the four events
- Set up a governing committee and carefully choose its chairman and members. Give the committee itself an appropriate level of funding.
- Set an approximate date for the first User-Interface Olympics.

If the User-Interface Olympics were to become successful (meaning it had the participation of many contestants and user interface designers, it spawned good new ideas in user interface design, it had become prestigious, and it had become financially self-supporting), the benefits which could be expected might include the following:

- rapid innovation in user-interface hardware and software
- recognition for inventors and engineers — on a par with scientists (Nobel Prize), writers (Pulitzer Prize), and actors (Academy Award)
- improved performance on the tasks chosen as events

Sometimes prizes can have an inordinately large effect in relation to the amount of money put up. Witness the prize for the first computer to beat the (human) world chess champion (Hsu 1998; Loviglio 1997). Witness the prize for the first human-powered flying machine (Brown et al. 2001). A million dollars or so in prize money to jump-start the User-Interface Olympics might be one of the best investments ever made.

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ACCELERATING CONVERGENCE OF NANOTECHNOLOGY, BIOTECHNOLOGY, AND INFORMATION TECHNOLOGY

Larry Todd Wilson, IEEE

My goal is to focus on a single NBIC-oriented idea that, if actualized, would unleash massive capabilities for improving all human performance. This single thing would have extreme interrelated, multiplicative effects. It's a bit like an explosion

that starts consequential, far-reaching chain reactions. Furthermore, the one thing should accelerate and strengthen all other biotech ideas and fulfill a self-referential quality for advancing itself. It is difficult to negate the notion that some ideas, actions, or objects are more important than others. This perspective is characterized by statements like, "This is what should come first because if we had that ability or understanding, then we could (achieve these results)… and if we had those results, then we could actualize…"

The "One Thing"is, *Nullify the constraints associated with a human's inherent ability to assimilate information.*

Why should this receive favorable positioning? Advances in thinking performance are more important than advances in artifacts. This is due to the fact that the advances in artifacts are always a function of the human thinking system. The dynamics of innovation must be managed by human consciousness before it is "externally" managed at all. There are many naturally occurring phenomena that are not apparent to the senses or the imagination. However, a technology does not become a technology until it enters the realm of human consciousness.

Examples below deliver "as-is" versus "could be" explanations of the importance of enhancing how we assimilate information. From the examples, it is not difficult to imagine the transformations that may result due to the ripple effects. Overall, the focus on ways to enhance how humans assimilate information will result in significant increases in a human's ability to approach a complex need, achieve comprehension, and accomplish an intended result. Increased ability equates to gaining faster comprehension, better comprehension, comprehension in a situation that previously was unfathomable, faster solutions, and better solutions, and to finding solutions to problems that seemed unsolvable.

Assimilating information is a kind of human intellectual performance. There are three and only three types of human performance that could be the focus of improvement:

- intellectual performance (such as thinking, deciding, learning, and remembering)
- physical performance (such as moving, reaching, and lifting)
- emotional performance (feeling)

All human experiences are variations of one or more of these three.

Candidates of the "best thing" could be evaluated according to either criteria or questions like these:

- Is this idea/action/object fundamental to all dimensions and expressions of human performance (thinking, feeling, and moving)?
- Does this thing have a multiplicative nature in regards to all other biotech ideas, actions, and objects? Does this one thing produce fission-oriented and fusion-oriented results? Does its presence cause a reaction that in turn creates energy associated with pragmatic NBIC inventions and discoveries?
- *A priori*, does it have validity on its face? Does a listener agree that this one thing will indeed impact everything else?
- *A posteriori*, does it have perceptible, significant advances in several other areas? Did this one thing deliver a high return on investment? How do we

know? What is measured? Does its presence actually increase the rate of all biotech inventions and discoveries?

Table B.1

AS IS	COULD BE
The span of judgment and the span of immediate memory impose severe limitations on the amount of information that we are able to receive, assimilate, and remember. In the mid-1950s, this was labeled as "seven, plus or minus two."	The innate limitations of human short-term memory are irrelevant due to the synergistic reliance upon "external" working memory, which is embedded in everything around us.
Short-term memory is working memory that works to retain sensory information presented by the mechanism of attention. No human being can hold many concepts in his head at one time. If he is dealing with more than a few, he must have some way to store and order these in an external medium, preferably a medium that can provide him with spatial patterns to associate the ordering, e.g., an ordered list of possible courses of action.	Increase the size and capability of working memory. Deliberate consideration of the items in external working memory can be called to mind upon demand. Manage how linguistic coding influences thought processes. Quantitatively measure stimulus (primarily in the form of linguistic-based prompts) and response (reactions in the form of decisions or feelings or movements).
Material is lost from short-term memory in two ways; it will not be committed to long-term memory if interference takes place or time decay occurs. One of the by-products related to the limitations of short-term memory is that there is great relief when information no longer needs to be retained. Short term memory is like a series of input and output buffers in which intermediate data can be stored during any thinking activity; this memory has very limited capacity and can be easily overloaded. In order to alleviate the anguish of overload, there is a powerful desire to complete a task, reduce the memory load, and gain relief. This event is referred to as "closure," which is the completion of a task leading to relief.	Minimize the losses that naturally occur. Consciously add or delete items in working memory. Regulate the need for closure because the human is confident that it's "still there" (although I don't remember exactly what *it* is). Increase the number and rate of working memory instances. Engineer a seamless human mind/external memory interface, and thereby make human and machine intelligence coextensive. Basic analysis and evaluation of working memory contents are achieved in partnership or alone.

AS IS	COULD BE
Bounded rationality refers to the limitations inherent in an individual's thought processes when there are more than a few alternatives being considered at the same time. Bounded rationality occurs because an individual has limited, imperfect knowledge and will seek satisfaction rather than strive for optimal decisions.	Effectively unbound "bounded rationality." The number and interrelationships of evaluations are dramatically expanded.
Individual thinking repertoires are limited (in their usefulness) and limiting (in their applicability).	Codify the elemental and compound thinking processes. Use the external working memory to manage the objects of the attention with novel ways of orchestrating the human's awareness of them. Increase the frequency, quantity (novel combinations), and throughput of these compounds. Gather more and more intelligence about the signals — the contextual nuances associated with variations of the compounds. Examples of compounds are Abstract Accept Accommodate Adopt Advise Agree Align Apply Appraise Approve Arrange Assign Assimilate Assume Authenticate Authorize Calculate Catalogue Categorize Change Check Choose Classify Close Compare Compile Compute Conclude Conduct Confirm Consider Consolidate Construct Contrast Contribute Coordinate Create Decide Decrease Deduce Define Delete Deliberate Deliver Deploy Derive Describe Determine Develop Differentiate Direct Disagree Disapprove Discern Distinguish Elaborate Eliminate Emphasize Enable Enhance Enrich Establish Estimate Examine Exclude Execute Expand Explore Extrapolate Facilitate Find Focus Formulate Generalize Group Guess Guide Hypothesize Imagine Include Incorporate Increase Index Induce Infer

AS IS	COULD BE
	Inform Initiate Insert Inspect Interpret Interview Invent Judge Locate Match Measure Memorize Merge Modify Monitor Observe Optimize Organize Originate Outline Pace Predict Prepare Presume Prevent Prioritize Probe Promote Provide Question Rank Rate Reason Receive Recognize Recommend Refine Reflect Regulate Reject Remove Report Resolve Respond Scan Schedule Scrutinize Search Seek Serve Settle Show Solicit Solve Sort Speculate Submit Support Suppose Survey Synthesize Translate Validate Verify Visualize.
Specialists often miss the point. The point is to swap advances among different disciplines. It's all about permutations and combinations. Discoveries from biology and chemistry are hooked up with synthesis and fabrication tools from engineering and physics. Each discipline has its own sets of problems, methods, social networks, and research practices. There are no effective ways in which the intellectual results of subdisciplines can be managed and thereby accelerate consilience and cross-disciplined performance breakthroughs.	Progress towards a new sense of the complex system. The most obvious change will be the benefits of working with many kinds of associations/relations. More people will be able to perceive loops and knots. Sense the complex system with a set of universal constructs for systematically managing the interrelationships among disciplines. Accurate visualization of many kinds of relations (not just parent-child relations) will shift the reliance of the satisficing mode of hierarchical interpretations to the closer-to-reality heterarchical structure. Continue to splinter the subdisciplines and achieve convergence when needed for important insights.
Today, many physicists spend time translating math into English. They hunt for metaphors that can serve as a basis for enhancing comprehension of relatively imperceptible physical phenomena.	Integrate mathematics, verbal, and visual languages in order to allow individuals to traverse the explanation space. Aid the acceleration of new ways for more people to abandon their intuitive (perhaps innate) mode of sensory perception associated with the macro world. Achieve integration (and concise translation) between our symbol sets

AS IS	COULD BE
	(math, verbal, and visual) and open up the chance to address more, apparently paradoxical, phenomena. The assumption is that many of these paradoxes are just illusions created when you look at an n-dimensional problem through a three-dimensional window.
Linguistic-based messages, which plod along the user's tolerance for listening, govern the rate of assimilation.	Establish the path more directly because all forms of intelligence, whether of sound or sight, have been reduced to the form of varying currents in an electric circuit.
Imaging modalities don't offer a concise way of observing the dynamics of how we assimilate information. PETs are more accurate in space, and EEGs are more accurate in time. EEGs can capture events on the scale of milliseconds, but they're only accurate to within centimeters. Scans are like slow motion — a thousand times slower — but they're accurate to the millionth of an inch.	Extend the visual languages to the actual visualization of localized neuronal activity. Understand the spatial-temporal nature of assimilation with a realtime movie stage where we watch thoughts as they gather and flow through the brain. Understand how the human perception of mind arises from the brain. Formalize in neural network models operating on traditional hardware. Thus, intelligences akin to humans will reside in the Internet. These intelligences, not being physically limited, will merge and transform themselves in novel ways. The notion of discrete intelligence will disappear.

C. IMPROVING HUMAN HEALTH AND PHYSICAL CAPABILITIES

THEME C SUMMARY

Panel: J. Bonadio, L. Cauller, B. Chance, P. Connolly, E. Garcia-Rill, R. Golledge, M. Heller, P.C. Johnson, K.A. Kang, A.P. Lee, R.R. Llinás, J.M. Loomis, V. Makarov, M.A.L. Nicolelis, L Parsons, A. Penz, A.T. Pope, J. Watson, G. Wolbring

The second NBIC theme is concerned with means to strengthen the physical or biological capabilities of individuals. The panel's work dovetailed with that of the first panel in the area of human cognition, especially the exciting and challenging field of brain performance. The *brain*, after all, is an organ of the human body and is the physical basis for that dynamic system of memory and cognition we call the *mind*. An extremely complex brain is the feature of human biology that distinguishes us from other animals, but all the other tissues and organs of the body are also essential to our existence and overall performance, and they thus deserve close scientific and technological attention.

The convergence of nano-bio-info-cogno technologies is bound to give us tremendous control over the well-being of the human body. In turn, it will change the way we think about health, disease, and how far we go to treat a patient. These new technologies will enable us to decipher the fundamental mechanisms of a living being, yet at the same time, they raise the fundamental questions of what life is and how human capability is defined. The panel gave highest priority to six technologies for the improvement of human health and capabilities in the next 10-20 years. In realizing these priorities, it will be essential to keep a "healthy" balance on human issues while seeking technological and social solutions.

1. Nano-Bio Processor

As the convergence of NBIC progresses, it will be imperative that the technology be focused on ways to help enhance human health and overall physical performance, be disseminated to a broad spectrum of the population, and be developed by a diverse group of scientists and engineers. One potential platform that will enable this would be a "bio-nano processor" for programming complex biological pathways on a chip that mimics responses of the human body and aids the development of corresponding treatments. An example would be the precise "decoration" of nanoparticles with a tailored dosage of biomolecules for the production of nanomedicines that target specific early biomarkers indicative of disease. The nanomedicine may be produced on one type of nano-bio processor and then tested on another that carries the relevant cellular mechanisms and resulting biomarker pathways. The nano-bio processor would parallel the microprocessor for electronics, such that the development of new processes, materials, and devices will not be limited to a handful of "nano specialists." With the advent of the nano-bio processor, knowledge from all fields (biology, chemistry, physics, engineering, mathematics) could be leveraged to enable advancements in a wide variety of applications that improve human health and enhance human capabilities.

2. Self-Monitoring of Physiological Well-Being and Dysfunction Using Nano Implant Devices

As the scales of nanofabrication and nanotransducers approach those of the critical biomolecular feature sizes, they give the technologist the toolset to probe and control biological functions at the most fundamental "life machinery" level. By the same token, this technology could profoundly affect the ways we manage our health.

One outcome of combining nanotechnology with biotechnology will be molecular prosthetics — nano components that can repair or replace defective cellular components such as ion channels or protein signaling receptors. Another result will be intracellular imaging, perhaps enabled by synthetic nano-materials that can act as contrast agents to highlight early disease markers in routine screening. Through self-delivered nano-medical intervention, patients in the future will be able in the comfort of their homes to perform noninvasive treatments autonomously or under remote supervision by physicians.

Metabolic and anatomical monitoring will be able to give humans the capability to track the energy balance of intake and consumption. Monitoring high-risk factors will be able to facilitate early diagnosis, when medical treatments can be most effective. Information systems designed to present medical data in ways that are intelligible to laypersons will allow anyone to monitor his or her health. As a result of NBIC-enabled "wonder medicines," there will be a need to develop technology and training modalities to make the patient an essential partner in the process of health monitoring and intervention.

As the population ages, more and more age-related diseases and deteriorating functions (e.g., hearing, memory, muscle strength, and sight) will be prevalent; an obvious example is Alzheimer's disease. Some of these dysfunctions are due to molecular changes over time, and some are due to the natural decay of bodily functions. NBIC will provide ways to slow down the aging process or even reverse it.

3. Nano-Medical Research and Intervention Monitoring and Robotics

The convergence of nano-bio-info-cogno technologies will enhance the toolset for medical research and allow medical intervention and monitoring through multifunctional nanorobots. For example, a nano brain surveillance camera could be developed. Imaging tools will be enhanced by nanomarkers as anchor points for hierarchical pinpointing in the brain. A range of nano-enabled unobtrusive tools will facilitate research on cognitive activities of the brain.

Nano-enabled unobtrusive tools will be invaluable for medical intervention, for example, nanorobots accomplishing entirely new kinds of surgery or carrying out traditional surgeries far less invasively than does a surgeon's scalpel. Technological convergence will also enhance post-surgery recovery. Although open surgical procedures will probably be reduced in numbers, the need for them will not be eliminated. Each procedure induces different side effects and risk factors. For instance, open-heart surgery increases the risk for stroke several days after the operation. NBIC technologies could enable devices that monitor such risk factors and immediately notify the physician at the first indication of a precursor to the onset of post-surgery traumas.

4. Multimodalities for Visual- and Hearing-Impaired

In the United States, there are eight million blind people and 80 million who are visually impaired. The current paradigm of electronic communication is visual and conducted through the use of monitors and keyboards. It will be important for NBIC technologists to address the need for multimodal platforms to communicate with, motivate, and utilize this population group. Examples of different modes of communication include talking environments and 3-D touch screens to enable access to the Internet.

While convergent technologies will benefit disabled persons, they in turn will contribute greatly to the development of the technology, thereby benefiting all people. In recognition of this fact, disabled scientists and engineers should be included in research and design teams. As NBIC blurs the boundaries of normal and abnormal, ethical and unethical, it will be important to include disabled members and advocates on advisory committees at all levels. This will include the private sector, academia, government, and international committees.

5. Brain-to-Brain and Brain-to-Machine Interfaces

The communication among people and between people and machines or tools has not been fully realized because of the indirect interactions. The external tools need to be manipulated as an independent extension of one's body in order to achieve the desired goal. If machines and devices could be incorporated into the "neural space" as an extension of one's muscles or senses, they could lead to unprecedented augmentation in human sensory, motor, cognitive, and communication performance.

A major goal is to measure and simulate processes from the neuron level and then to develop interfaces to interact with the neural system. A visionary project by Llinás and Makarov proposes a nonintrusive retrievable cardiovascular approach to measure neuron and group-of-neuron activities, and on this basis, to develop two-way direct human communication and man-machine telepresence.

Another goal is to establish direct links between neuronal tissue and machines that would allow direct control of mechanical, electronic, and even virtual objects as if they were extensions of human bodies. Another visionary project by Nicolelis proposes electrophysiological methods to extract information about intentional brain processes and then translate the neural signals into models that are able to control external devices.

6. Virtual Environments

Nanotechnology will permit information technology to create realistic virtual environments and geographies. And biotechnology guided by cognitive science will produce interfaces that will allow humans to experience these environments intensely. Thus, the union of these technologies will transcend the biological limitations of human senses and create a new human relationship to the physical environment. It will be possible to simulate in humans the sensation of being at remote locations or at imaginary new buildings or facilities. This could be used for rapid design and testing of large projects, thereby saving the cost of errors. Other economically significant applications could be in the entertainment industry, and the tourist industry could use the technology to provide virtual samples of distant locations to prospective customers.

Applications of special relevance to improving health and enhancing human physical abilities include the use of virtual environments for education and interactive teaching. This will provide new ways for medical students to visualize, touch, enter, smell, and hear the human anatomy, physiological functions, and medical procedures, as if they were either the physician or a microscopic blood cell traveling through the body. Similarly, impaired users, ordinary people, athletic coaches, and a range of health-related professionals could train in these virtual environments.

Statements and Visions

Participants in the panel on human health and physical capabilities contributed statements and visions on a wide range of technological challenges and opportunities. Several contributors addressed life extension (P. Connolly); therapeutics at the cellular level (M.J. Heller, J. Bonadio), physiological level (A.T. Pope), and brain levels (B. Chance and K.A. Kang, E. Garcia-Rill, L. Cauller and A. Penz); as well as brain-machine interaction (R.R. Llinás and V. Makarov, M.A.L. Nicolelis) and improving the quality of life of disabled people (G. Wolbring and R. Golledge).

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STATEMENTS

NANOBIOTECHNOLOGY AND LIFE EXTENSION

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This paper concentrates on only one of the complex debates emerging due to the convergence of nano-bio-info-cogno (NBIC) and the ability to improve human performance: that is, how nanobiotechnology will affect life extension. To deal with this in a comprehensive manner, the concept of life extension will be discussed, along with a brief presentation of the major obstacles that can be defined from our current knowledge in bioscience and medicine. It is proposed that a successful strategy for the convergence of NBIC disciplines in human terms will require a holistic approach and consideration of the full pathway from the human, down through organ, cell, and molecule, analyzing where NBIC can successfully intervene in this complex cascade. Some examples are given of areas where nanobiotechnology has had, or could have, impact in the problem areas of human well-being and quality of life as they are understood today.

Life Extension and Nanobiotechnology: Some Key Criteria

Nanobiotechnology for the purposes of this discussion is defined as the application of nanotechnology or nanobiology to a biological environment that involves device or material interactions with biological or biomolecular systems. To consider nanobiotechnology and life extension, it is important to first consider

which social groups might be targeted by this approach and then to examine their medical and social requirements, highlighting where the NBIC convergence will have an effect. For example, the problems of the developed and developing world are quite different in terms of life extension. The problem of environmental damage and rising world pollution threatens the quality and length of life span of both groups. Table C.1 summarizes some of the major problems that must be addressed in extending life in developed and developing countries (WHO 1998a; WHO 1998b; WHO 2000; WHO 2001).

Table C.1
The Challenges to Life Extension in Developed and Developing Countries

Target Groups	Quality of Life Problems	Major Causes of Death and Disability
Developed Countries: Aging Populations only	• Loss of strength and mobility • Loss of mental sharpness / neurological disease • Social isolation • Poverty	• Cardiovascular Disease • Diabetes and its complications • Inflammatory diseases including arthritis • Cancer • Neurological Disease or Impairment
Developing Countries: All age groups	• Environmental, lack of safe water & sanitation • Disease related loss of earnings • Poverty	• Malnutrition • Infectious diseases • Parasites • Cardiovascular disease

Governments in the developed world, including the United Kingdom (UK Foresight Consultation Document 1999), have started to develop an awareness of the needs of the increasingly aged populations that they have and will have in the first half of this century. Major disease groups or medical conditions that are the major causes of death or disability in the aging populations of the developed countries of the world have been identified. For example, according to the World Health Organization (WHO 2000), in 1999 around 30 percent of deaths worldwide were caused by cardiovascular disease and 12 percent by cancer.

The problems of the developing world are quite different, and it might be argued that unless life extension in this environment is addressed by those who have the technology and wealth to do so, then the stability of developed societies worldwide will be affected. The medical problems of developing countries are widespread: many of these could be resolved by improvement in economic factors; however, some problems, such as parasitic infections, have eluded complete medical solutions. Toxoplasma infects 50 percent of the world population and leads to miscarriage, blindness, and mental retardation. The WHO (1998b) states that one child dies in the world every 30 seconds from malaria. There is much scope for

improvement in the formulation of drugs, delivery modes, diagnostics, and effective vaccines for these and other diseases.

In addition, it is recognized that increasing levels of pollution with their consequent environmental changes drive aspects of both childhood and adult disease. The epidemiology of the disease patterns are being studied (WHO 2001), and nations are considering their role in reducing environmental emissions (EIA 1998). Nanobiotechnology may have a part to play here in land and water treatments through bioremediation strategies and in novel processes for industrial manufacture.

A Holistic Approach to Problem Definition

To effectively target emerging NBIC technologies, and in particular to make the most of the emerging field of nanobiotechnology, requires a strategic approach to identifying the problem areas in life extension. Biomedical problems currently exist on macro, micro, and nanoscales, and solutions to some apparently straightforward problems could enormously increase life expectancy and quality of life. A holistic approach would examine the key medical problems in the world's population that need to be solved to extend life, and at the same time, would consider the social environment in the aging population to ensure that quality of life and dignity are sustained after technological intervention.

A key element of this top-down approach is to consider the whole human being and not merely the immediate interface of nanobiotechnology with its target problem. The ability to view the needs in this area from a biomedical perspective that starts with the whole human and works down through organ and cellular levels to the molecular (nanoscale) level, will be an essential component of projects with successful outcomes in this field. There is little point in developing isolated, advanced technological systems or medical treatments to find that they solve one problem only to generate many others. For example, ingenious microdevices with nanoscale features that might patrol blood vessels or carry out tissue repairs have been suggested and designed (Moore 2001; Dario et al. 2000). However, there has been little detailed discussion or consideration at this stage regarding biocompatibility issues, particularly of the thrombogenicity (clot-forming potential) of these devices or of their immunogenicity (ability to stimulate an unwanted immune response). In this area, as in many others, there is a need for multidisciplinary teams to work together from the outset of projects to bring medicine and technology together. Ideally, these research teams would include clinicians, biomedical scientists, and engineers rather than being technologist-led projects that ignore much of the vast wealth of information we have already discovered about the human body through medical and biomedical research.

Accepting this need for biomedically informed project design also leads to the conclusion that understanding the cell-molecule interface, in other words the micro-nanoscale interactions, will be a factor in the extended application of nanobiotechnology. To create a holistic approach to widespread and successful introduction of nanobiotechnologies in life extension will require interdisciplinary teams and exchange of information. Figure C.1 illustrates the possible levels of intervention and some of the emerging solutions where nanobiotechnology will have a role in repair or replacement of damaged elements.

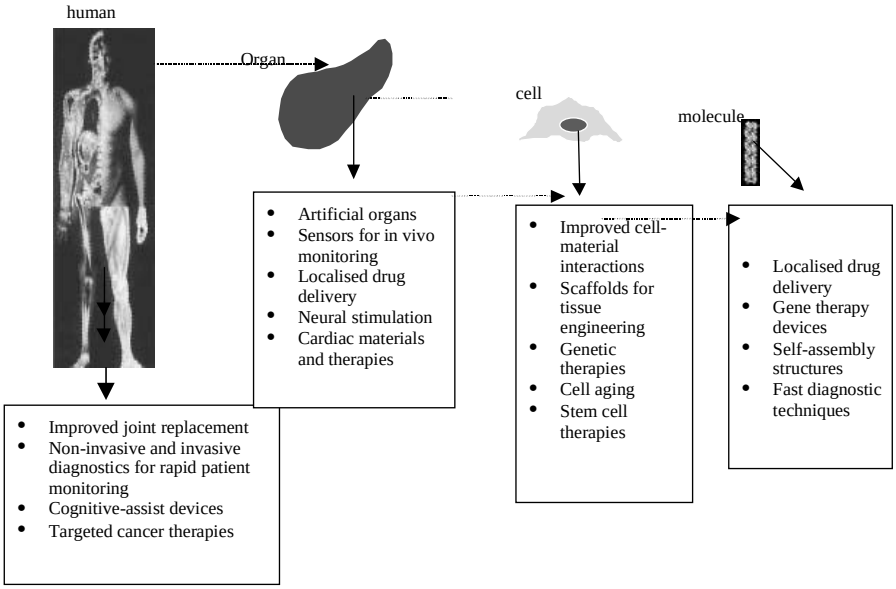

Figure C.1. Examples of levels for intervention of nanobiotechnology in human life extension.

The Need for a Holistic Approach: Some Specific Problems

As previously stated, there are a number of identified medical challenges that might benefit from intervention with nanobiotechnology. Many of these are long-term problems that have not been resolved by current technological or medical solutions. The following section is intended to briefly introduce some of these problems.

The Human-Materials Interface

Many of the disease conditions in the human body, and deaths during surgical intervention, can be traced to the body's in-built ability to react to foreign materials or wound sites through its inflammatory response. In normal disease or wounds, this ensures the proper activation of the immune response or of a clotting response from coagulation factors in blood. In extreme conditions or at chronic wound sites, the cascade reaction triggers a full inflammatory response that is harmful to tissue. In cardiovascular surgery, for example, reaction to physical intervention and surgical materials can lead to Systemic Inflammatory Response Syndrome (SIRS), and in a small percentage of cases, this will in turn lead to multiple organ failure and death (Khan, Spychal, and Pooni 1997).

The appearance of an inflammatory response following blood contact with a biomaterial can be readily measured in the molecular markers that are generated during the response, such as cytokines. (Weerasinghe and Taylor 1998). The reasons for the inflammatory response lie in molecular and cellular reactions at foreign surfaces. Nanobiotechnology could contribute to this field, both in terms of increasing the understanding of how the nanoscale events take place on particular

materials and in terms of creating new, more biocompatible surfaces for use in surgery.

An extension of these problems is the continued reaction of the human body to any artificial implant, no matter how apparently inert the material. For the aging population, this has direct consequences as joints and tissues (such as heart valves) require replacement. Implanted replacement joints such as hip joints still suffer unacceptably high failure rates and shorter implantation life cycles than are ideal in an increasingly aged U.S. and European population. Hip implant rejection and loosening is caused by the interaction of cells with the coating or surface of the implant (Harris 1995). This can be modified, but not entirely halted, by drug interaction. The patient's cells react to both the materials and the micro- and nanoscale surface features of the implant.

Nanobiotechnology has a place in the improvement of materials for surgery and implantation, both in the biological modification of surfaces to ensure that they do not degrade in use and in the study and manipulation of nanoscale topographies that directly influence cell movement and growth.

Neurological Disease

Both cellular decay and diseases such as Alzheimer's and Parkinson's contribute to loss of neural function, cognitive thought, and independence. In addition, events such as stroke leave many of the older population with impaired functions. It is here that implantable devices and cognitive science will have the greatest part to play in enhancing the quality of extended life.

Microdevices for cell-electrode interfacing for both cardiac and neural cells have been available for *in vitro* applications for many years. There are few examples of implanted systems. Some micro-array type devices have been implanted, for example, in rudimentary artificial vision systems (Greenberg 2000). On a slightly larger scale, electrode systems have been implanted in the brain to provide electrical signal patterns that alleviate some symptoms of Parkinson's disease (Activa®, Medtronic, Inc., USA).

Much remains to be done in neurological device development, including devising smaller systems capable of withstanding long-term implantation. Investigation of the submicron (synaptic) interface to devices from neurons may be an important area for consideration in this field. In the longer term, it may be that some conditions will be alleviated by local electrode and drug-release systems, but how to keep these devices in place for years so that they remain biologically or electrically viable remains a difficult problem. There will be a need to develop sub-micron arrays of electrodes and chemo-arrays in devices designed to replace diseased tissue. If nanoscale electrode-cell interactions are expected to be important, then a fuller understanding of the cell-nanoelectrode interface will be required both *in vitro* and *in vivo*.

Cell replacement technologies are also being developed to address neural decay, and success with this type of approach, such as stem cells (see discussion of artificial organs and tissue engineering below), may remove the need for extensive device development. Cell placement and growth techniques may still, however, require device intervention and nanobiotechnology know-how.

Artificial Organs and Tissue Engineering

In the field of tissue repair and replacement, advances are being made in the creation of artificial organs and replacement tissue. In the case of artificial organs, many of the components of the organ will not be linked to the body's own regulatory systems (e.g., artificial heart pumps). In engineered tissue for repair or replacement of damaged tissue, control of tissue growth and tissue integration are critical and will require monitoring.

To provide sensitive feedback control to artificial organs either within or external to the body (such as the artificial liver), biosensor systems will be required, perhaps coupled to drug or metabolite delivery systems. This is an ongoing problem, since no long-term implantation systems based on biosensors have become commercially available, even with the application of microtechnology (Moore 2001; Dario et al. 2000) — although improvements have been made for subcutaneous glucose sensors in recent years (Pickup 1999). There is opportunity here for the use of nanobiotechnology to both provide the sensors for monitoring and adjusting organ performance and to aid localized drug or metabolite delivery to artificial organs. It may be possible to create biosensors for long-term implantation by trapping "factory cells" in gels within the sensor system, which would, in turn, synthesize any required renewable nanocomponents in the sensors, thus avoiding the current problems of sensor degradation over time.

Significant amounts of time, money, and research effort are being directed to the field of tissue engineering for skin, cartilage, bone, and heart tissue regeneration or repair, as well as for other types of tissue. Biopolymer scaffolds are the material of choice for the seeding of cells to grow replacement tissue. At the macro or fiber level, much is known about these scaffolds, but little time has been devoted to the nanoscale effects of topography or surface molecular treatments that could be influenced by nanobiotechnology. Nanovesicles that could be incorporated into tissue scaffold structures for slow release of chemoattractants could greatly improve tissue uptake or repair. One group has recently successfully exploited the idea of self-assembly of molecules, in this case, peptide-amphiphile molecules, to create biopolymer scaffolds with nanoscale features for bone repair (Hartgerink, Beniah, and Stupp 2001). This group's experiments show that a key constituent of bone, hydroxyapatite, can be made to grow and align in the same manner as bone *in vivo* using these scaffolds.

Stem cell research promises to open up new possibilities for harvesting cells that can be transformed *in situ* into different tissue types for repair or regeneration of damaged tissue. This may require extensive technological intervention both for harvesting cells and in delivering cells for therapy.

Genetic Techniques

The explosion in the field of genetics has led to the availability of a range of diagnostic tests for predisposition to illnesses, including cancer, although final expression of many illnesses may have strong environmental factors that must be taken into account. Together with the possibility of gene therapy for specific diseases, this offers new hope of life extension to many people. For example, hereditary lung conditions such as cystic fibrosis are being targeted by gene therapy to replace missing or deficient genes (Douglas and Curiel 1998). Study of how cells

age is being taken up by many research groups and, again, offers hope for many potential victims of cancer and degenerative disease. Nevertheless, any widespread genetic intervention in disease is still some way off. To quote one recent review paper, "Ideally, gene therapy should be efficient, cell-specific, and safe (Hu and Pathak 2000). One of the challenges of gene therapy is the efficient delivery of genes to target cells. Although the nucleic acids containing the genes can be generated in the laboratory with relative ease, the delivery of these materials into a specific set of cells in the body is far from simple." It is perhaps here in the design and development of efficient delivery devices and systems that nanobiotechnology will play its biggest role in gene therapy.

Drug Delivery

There are still many opportunities for nanobiotechnology in the field of drug delivery, particularly in delivery of those drugs unsuitable for the gastrointestinal system. Skin and lungs have become favorite alternative routes for drug delivery, with nanovesicles and microcrystals as popular drug carriers (Langer 1999). Cancer treatment has yet to fully benefit from the targeted delivery to tumors of drugs in microdevices with local nanoscale interactions. Likewise, cancer monitoring and surgery would benefit enormously from miniaturized sensor or other diagnostics systems that could be used in the pre-, peri-, and postoperative environment.

The Prospects for Life Extension

Any quantitative discussion on the prospects for life extension through nanobiotechnology intervention in disease must be purely hypothetical at this stage. However, speculating across the human-organ-cell-molecule model may give some idea of the possible times to application of some of the approaches under development. Table C.2 summarizes what is a very personal view of the likely outcome of convergence in NBIC.

Visions for the Future

Loss of mobility and therefore independence is critical in the onset of decay and isolation for many older people, and one area in the developed world where people are very dependent for mobility is in the use of a car. Confidence and cognizance decline for many people as they age; in the car of the future there is the possibility to see the true convergence of NBIC in extending independence and warding off part of the decline in the older person. Higher-speed, higher-density computers and effective sensors driven by nanotechnology may combine with on-board artificial intelligence in the car, helping the driver plan routes and avoid hazards and difficult traffic situations. Nanobiotechnology may also be present in on-board minimally invasive biosensors to monitor the driver's health, both in terms of physical stress and physiological condition, to be fed back to the car's computer. In a further interpretation, since the possibility of implanted devices to stimulate or improve cognizance are emerging, the driver may also benefit from neuronal stimulation designed to keep him or her alert and performing optimally during the trip.

Table C.2
Some Potential Gains in Life Extension from NBIC convergence

Level of Intervention	Key Advance	Timescale (years)	Life Extension
Human	Noninvasive diagnostics	5-10	Lifesaving for some conditions
	Cognitive assist devices	15-20	Higher quality of life for several years
	Targeted cancer therapies	5-10	Reduction in cancer deaths by up to 30%
Organ	Artificial heart	0-5	2-3 years awaiting transplant
	Neural stimulation or cell function replacement	5-20	10-20 years extra if successful for neurodegenerative patients
Cell	Improved cell-materials interactions	0-15	Lowering of death rates on invasive surgery by 10% and extending life of surgical implants to patient's lifetime
	Genetic therapies	30	Gains in the fight against cancer and hereditary diseases
	Stem cells	5-10	Tissue / brain repair Life extension of 10-20 years
Molecule	Localized drug delivery	0-10	Extending life through efficient drug targeting
	Genetic interventions	0-30	Life extension by targeting cell changes and aging in the fight against disease Likely to be a very complex environment to successfully manipulate

The convergence of NBIC in the field of life extension will lead to implanted devices such as sensors and drug delivery systems being developed to replace or monitor body function. Implanted devices, whether macro or micro in scale, present a problem today in terms of biocompatibility. Implantation of a heart valve in a patient means that a drug regime for anti-coagulation is mandatory — usually through administration of warfarin. Since inflammatory response and immunogenic response take place *in vivo,* many of the devices being discussed and designed today to improve human performance incorporating nanotechnology will not be implantable because of biocompatibility issues. A further complication will be how to keep a nanodevice biologically or electronically active (or both) during sustained periods of operation *in vivo*. Sustained exposure to physiological fluid, with its high salt and water content, destroys most electronic devices. Likewise, devices that emit biological molecules or are coated with biological molecules to ensure initial biocompatibility must have their biological components renewed or be destined to become nonfunctional some time after implantation. Little attention is being given

to these problems, which may prove major stumbling blocks in the next 10-30 years to the successful application of nanotechnology in a range of medical conditions.

A "holistic human project" could bring together the best research clinicians, biomedical engineers, and biomedical scientists to discuss the main life-shortening diseases and conditions and current progress or problems in their treatment or eradication. Together with the nanotechnologists, areas where conventional medicine has not been successful could be identified as strategic targets for nanobiotechnology. Specific project calls could follow in these areas, with the condition that the applicants' teams must show sufficient interdisciplinary interaction to provide a comprehensive understanding of the nature of the problem. The opportunities are immense, but the resources available are not unlimited, and only strategic planning for project groups and project themes will realize the maximum benefit for biomedicine and society.

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THE NANO-BIO CONNECTION AND ITS IMPLICATION FOR HUMAN PERFORMANCE

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Many aspects of nanotechnology will lead to significant improvements in human performance; however, the nano-bio area will be particularly important and relevant to such improvements. Technological advancements in the past decade have been nothing short of phenomenal. These advancements have led to an increasingly better understanding of human biology. We can expect that the new advancements in the nano-bio area will not just lead to a better understanding of human biology, but will also provide a new dimension and capability to affect human biology. The fact we are having this workshop and all know its true importance and underlying implications speaks for itself.

Individualized Treatment for Human Development

How nano-bio technologies will be applied in the most beneficial ways is dependent on the underlying basis for human performance. It is very likely that most of the underlying basis is genetic in origin (Wexler 1992; Ridley 2000). While this may still be widely debated and resisted for other reasons, it will (when proven) have profound implications, and it certainly needs to be considered in any planning on new technology application in human biology. The following is an example, which will hopefully not trivialize the issue.

Many individuals greatly enjoy a variety of sporting activities. However, a vast majority of individuals who do any of these sporting activities cannot approach the capabilities of a professional player, even with all the best new technology, instruction, and personal motivation. While some might feel this unfair, most people accept it and keep it in perspective. After all, people in general usually have something they do well, even if they never develop the desired trait. Not only is this true for athletic capabilities, but this is widely observed for other capabilities such as talent in art or music. Until recently, these perceptions were not based on any real scientific evidence. Now, with the first phase of the human genome project complete and a new geomics revolution occurring, good evidence is appearing that many human performance traits do indeed have a genetic basis.

This may also hold true for human behavior (Chorney et al. 1998; Dubnau and Tully 1998). Just a few years ago psychiatrists and psychologists would have doubted the genetic basis for many of the important mental illnesses. Today, there are few diseases left that are not known to be directly or indirectly genetically based (Kamboh 1995; Corder et al. 1994). Even infectious diseases are not really an exception to this premise, as there are always individuals who have a positive genetic component that provides varying degrees of resistance to the infection (Hill 1996).

A particularly relevant example of the importance of understanding the true basis of “cause and effect” in determining technological strategy now comes from the pharmaceutical industry. The new area of phamacogenomics is now proving for one drug after another that so-called drug toxicity is really based upon individual genetic polymorphisms. Usually, for any given drug, there are always a small number of individuals for whom that drug is toxic or less effective. As the genes and pathways

for drug metabolism are better understood, this drug toxicity is usually found to correlate in some fashion with single nucleotide polymorphisms (point mutations) in the affected individuals. Not too long ago, most drug companies were investing huge amounts of money looking for "safe" drugs. Today, most accept or will soon accept the fact that patient stratification (via either genotyping or phenotyping) will be necessary to determine drug toxicity.

This represents a key example of how important it is to properly identify cause and effect in relation to technology development. The pharmaceutical industry spends enormous amounts of money developing new drugs, and many potentially useful drugs are being delayed or not used because they have serious toxicity for a small number of individuals. This also presents a view of how genetic determination is misunderstood. If we were to look at just a single drug, genetic testing of potential drug recipients would seem totally unfair and appear that genetic testing is being used to exclude some individuals from a potential benefit — even though some individuals truly don't benefit from that particular drug. However, at least in the area of therapeutics, we do not have to look at too many drugs until we find that, in general, the vast majority of humans will always have one or two important drugs that are not beneficial or are harmful to them. The lesson here is that it does not do a lot of good to pump enormous amounts of money into developing technology for new drug discovery without patient stratification — and this is genetics.

We should probably expect the same scenario to develop for human performance, and also, whether we like it or not, for human behavior.

Thus, now is really the time for scientists to put this issue into proper perspective. The misconception and fears about genetic determination are so misguided that we are delaying technology that can actually help improve existence for everyone. In medical diagnostic areas, we accept without any reservations tests and assays that try to determine whether we have a disease and the state of that disease. However, many people view with great concern genetic testing that is more direct and provides earlier detection. There are most certainly very important ethical issues relevant to the genetic determination. But even these are in some sense clouded by misconceptions, due to past behavior by groups who misunderstood the real meaning of genetic determination and/or intended to misuse it. It is time to correct this and gain the full benefits of our technology for everyone.

Tentative Plan for Understanding Genotype and Performance

We should start with the premise that almost every (physical) performance trait will be related to some distinct group of genotypes. (Genotypes from outside the group can also influence the trait, but this does not change the basic premise). This group of related genotypes will usually present itself in the general population as most individuals having average performance, some individuals having below-average performance, and another group of individuals having above-average performance. If we were to take "*running"* as an example, we can already begin to scientifically relate this trait to genetic polymorphisms in muscle tissue as well as other physiological characteristics. Even though we will ultimately identify the related group of genotypes that can accurately predict the performance level for any given physical trait, several problems do exist. The first problem is that there is considerable complexity in how different traits combine to affect "overall"

performance. The second problem is to determine how these combinations of traits influence overall performance under different environmental challenges or stresses.

The goals for an initial plan to evaluate genotype and performance are listed below:

1. Begin to correlate physical (and related behavioral) performance characteristics with the genotypes and polymorphisms that are rapidly emerging from the human genome project. This would not be much different from what pharmaceutical companies are doing related to patient stratification for drug toxicity effects.
2. Begin to model how combinations of traits influence overall performance. Then separate the groups of directly related genotypes from those that indirectly influence the trait.
3. Begin to model and understand how a higher performance trait (or traits) that provide(s) an advantage under one set of environmental conditions and/or challenges, is not an advantage or is even a disadvantage under another set of environmental conditions and/or challenges.

This third point is probably the most difficult to deal with, because it leads to diversionary semantic and philosophical questions as to whether biology (genetics) or environment is in control, and what is cause and what is effect. These questions will be put into better perspective using examples of genetic disease in the human population (Jorder et al. 2000) and examples of how particular "types" of stress relate to heart disease (Ridley 2000; Marmot et al. 1991).

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GENE THERAPY: REINVENTING THE WHEEL OR USEFUL ADJUNCT TO EXISTING PARADIGMS?

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The availability of the human genome sequence should (a) improve our understanding of disease processes, (b) improve diagnostic testing for disease-susceptibility genes, and (c) allow for individually tailored treatments for common diseases. However, recent analyses suggest that the abundance of anticipated drug targets (yielded by the genome data) will acutely increase pharmaceutical R&D costs, straining the financial outlook of some companies. Therefore, to stay competitive, companies must couple a threshold infrastructure investment with more cost-effective validation/development technology. However, no such technology currently exists.

This paper discusses the potential advantages and disadvantages of gene therapy as a validation/delivery platform for the genomics era. Gene therapy is the use of recombinant DNA as a biologic substance for therapeutic purposes. Although significant technological hurdles exist, for certain drug targets the potential for gene therapy as a validation/delivery platform is enormous. Thus, one may see

- direct, efficient transitions from database query to preclinical validation to lead drug candidate development
- significant improvements in the patient care pathway of important common diseases such as cancer, diabetes, and osteoporosis; these improvements would be expected to yield improved compliance and significantly better control of disease manifestations

The vision is that in 10 to15 years, the U.S. private sector will have a drug discovery and development pathway that is significantly more cost-effective than what exists now and therefore is capable of taking full advantage of the promise of the human genome database. If this vision is realized, one can easily imagine that the process of transferring advances in drug development from the developed world to the undeveloped world will be significantly enhanced.

To traverse the technological hurdles associated with this vision, an interdisciplinary spirit will be required to advance our knowledge base in basic science and drug development, e.g., geneticists will (again) need to talk to physicists, physiologists to chemists, and cell biologists to engineers.

Drug Development Trends: Personalized Medicines

Human health is determined by the satisfaction of basic needs such as food and the avoidance of serious hazards such as trauma, environmental change, or economic disruption. In the world today, we find examples of almost all forms of social organization that have ever existed, including communities of hunter-gatherers, nomadic pastoralists, and primitive agriculturalists; unhygienic, large cities in the third world; and the modern, large cities of the developed world. This variation in living conditions is associated with differing patterns of human disease around the globe (McKeown 1988) as well as with patterns that shift in a dynamic manner, creating a rather large and varied number of therapeutic targets for the pharmaceutical industry to consider.

In contrast to the dynamic and varied patterns of human disease worldwide, the pharmaceutical industry has a long history of pursuing only those limited number of human proteins (G-protein coupled receptors, ion channels, nuclear hormone receptors, proteases, kinases, integrins, and DNA processing enzymes) that make the best drug targets (Wilson et al. 2001). Even so, a high percentage of drug candidates never reach the market because adverse reactions develop in a significant percentage of individuals, while many approved drugs are effective for only a fraction of the population in which they are prescribed. This variation in drug response depends on many factors, including gender, age, genetic background, lifestyle, living conditions, and co-morbidity.

Since the 1950s, pharmacogenetic studies have systematically identified allelic variants at genetic loci for relevant drug-metabolizing enzymes and drug targets (Evans and Relling 1999). These studies suggest that genetic tests may predict an individual's response to specific drugs and thereby allow medicines to be personalized to specific genetic backgrounds. For some drugs, the geographic distribution of allelic variants helps explain the differences in drug response across populations. The frequency of genetic polymorphisms in drug-metabolizing enzymes, which contribute significantly to phenotype, may vary among populations by as much as twelve-fold. For example, between 5 percent and 10 percent of Europeans, but only 1 percent of Japanese, have loss-of-function variants at *CYP2D6* (debrisoquine oxidation) that affect the metabolism of commonly used agents such as beta-blockers, codeine, and tricyclic antidepressants. Polymorphisms in drug-metabolizing enzymes can lead to acute toxic responses, unwanted drug–drug interactions, and therapeutic failure from augmented drug metabolism (Meyer and Zanger 1997). Therefore, one approach to drug development in the future may be to test candidate formulations in populations that are genetically homogenous for certain key genetic markers. Still, specific research challenges remain as to the most appropriate way to catalog human genetic variation and relate the inferred genetic structure to the drug response.

Impact of Genome Analysis Technology

The preceding 50 years have been a time of rapid and profound technological change. The elucidation of the genetic flow of biological information (i.e., information flow from DNA to RNA to protein) has provided a basis for the development of recombinant DNA technology; the rise of molecular cell biology; the advent of intellectual property in biology and medicine); the development of the biotechnology industry; the development of transgenic technologies (including human gene therapy); the elucidation of the modern definition of stem cells; and the advent of cloning technology. Arguably, the defining technological event of the last few years has been the development and large-scale implementation of tools for the global analysis of genomes. Less than a decade ago, it was relatively uncommon to have full-length cDNAs at hand for experimental purposes. Within a decade, it may be commonplace to freely access the atomic structure of proteins, often in the context of their molecular partners. We have entered a new era of life science discovery research in which structure-function relationships form the basis of our understanding of cellular physiology and pathology (Ideker, Galitski, and Hood 2001).

We have also entered a new era of pharmaceutical discovery in which structure-function relationships underlie the search for new therapies (Dry, McCarthy, and Harris 2001). Thus,

- *We still do not know how the transcription machinery regulates gene expression* (Strausberg and Riggins n.d.), despite the fact that the scientific literature richly describes the presence and functional significance of alternatively processed human transcripts — as derived from different transcription initiation sites, alternative exon splicing, and multiple polyadenylation sites. Therefore, genome sequences must be annotated and additional databases of information must be developed.

  Large-scale analysis of gene expression originates from the expressed sequence tag (EST) concept. In the EST approach, a unique identifier is assigned to each cDNA in a library. Sequence tags of more than 700 nucleotides are now common, and the EST approach has been aided by formation of the IMAGE consortium, an academic-industrial partnership designed to distribute clones. The Merck Gene Index and the Cancer Genome Anatomy Project have produced many of the human clones distributed through the IMAGE consortium (http://image.llnl.gov/).

  Imaginative new strategies complement the traditional EST approach. One of these, "serial analysis of gene expression" (Velculescu, Vogelstein, and Kinzler 2000), produces sequence tags (usually 14-nucleotides in length) located near defined restriction sites in cDNA. One advantage of this method is that each transcript has a unique tag, thereby facilitating transcript quantification. Tags are concatemerized, such that 30 or more gene tags can be read from a single sequencing lane, which also facilitates the effort to catalog genes. The Cancer Genome Anatomy Project, working together with the National Center for Biotechnology Information, has generated a SAGE database, SAGEmap, that includes over 4,000,000 gene tags. To proceed effectively with transcriptome efforts, there has been a significant shift in emphasis toward the sequencing of complete human transcripts.

  In this regard, in 1999 the National Institutes of Health announced the Mammalian Gene Collection Project (http://mgc.nci.nih.gov), which aims to identify and sequence human and mouse full-length cDNAs. To date, that project has produced over 5,000 human sequences (deposited in GenBank). The German Genome Project recently completed full-ORF human cDNA sequences derived from 1,500 human genes.

- *Functional genomics may provide a mechanism to understand how proteins collaborate in an integrated, regulated, adaptive manner*. Multiple technologies support the field of proteomics, including genomics, microarrays, new mass spectrometry approaches, global two-hybrid techniques, and innovative computational tools and methods (Fields 2001). Protein localization within cells is now feasible at a genomic level. For example, thousands of yeast strains were generated recently in which more than 2000 *S. cerevisiae* genes were marked by transposon tagging (Ross-Macdonald et al. 1999). Indirect immunofluorescence was used to determine the subcellular localization for over 1,300 of the tagged proteins.

Increasingly, proteomic strategies afford the opportunity for quantitative analysis of the cellular response to environmental change. Advances in direct analysis by mass spectrometry of peptide mixtures generated by the digestion of complex protein samples have led to an escalating number of protein identifications in one experiment. These and other advances suggest that human tissues one day may be evaluated this way to advance our understanding of disease etiology and pathogenesis.

Finally, protein expression and purification technologies will continue to improve, and procedures that make use of protein arrays will become commonplace. Potential applications include revealing interactions among proteins and between proteins and small molecules (drugs) or other ligands. The promise of this approach was suggested by the recent demonstration of proteins in nanoliter droplets immobilized by covalent attachment to glass slides: more than 10,000 samples could be spotted and assayed per slide with this technique (MacBeath and Schreiber 2001).

A shift from genomics to proteomics is likely to be complicated, because single genetic loci may yield multiple polypeptides; proteins may change conformation in order to carry out a particular function; protein levels often do not reflect mRNA levels; proteins may undergo post-translational modification and proteolysis; and the presence of an open reading frame does not guarantee the existence of a protein. Proteins may also adjust their stability, change locations in the cell, and swap binding partners.

Finally, protein function may depend on context, i.e., the function of an individual protein may be determined by the entire set of proteins operating in a microenvironment at a particular point in time — the concept of protein pleiotropism (Sporn 1999). When taken together, these considerations suggest that the proteome may be an order of magnitude more complex than the genome (Fields 2001; Hol 2000).

- *Structural genomics promises to capitalize upon numerous advances in cloning, protein expression, protein purification, characterization, crystallization, crystal drop inspection, crystal mounting, model building, and NMR spectra interpretation*, although high-throughput structure determination of drug candidates is not yet available (Russell and Eggleston 2000). With the potential to impact heavily on the design of new pharmaceuticals, structural genomics will take a place alongside high-throughput chemistry and screening as an integral platform approach underpinning modern drug discovery. Like the large-scale genomic sequencing projects that have been running for more than a decade, this will involve profound changes in thinking and approach. Instead of developing a specific biological justification in advance of working on a protein, crystallographers and NMR spectroscopists can now consider the determination of structures for all proteins in an organism.

  Bioinformatics will play several roles in structural genomics. Target selection involves database interrogation, sequence comparison, and fold recognition in order to aid selection of the best candidate proteins given a particular set of requirements, e.g., disease-associated genes, or those that are common to most organisms. Solved structures must be placed in an appropriate genomic context and annotated so that functional details may be

predicted. Structural annotation may prove tricky, since large numbers of proteins of known structure but of unknown function have not previously been a major issue. Comparative modeling plays an essential role by providing structures for homologs of those determined experimentally, and efficient archiving of structural information is essential if the biological community is to make best use of all data. Given the biological and technological complexity associated with genome analysis technology, an interdisciplinary spirit will be essential to advance our knowledge base in basic science and drug development.

Drug Development in the Era of Genome Analysis: Applied Genomics

From SNP maps to individual drug response profiling, the human genome sequence should improve diagnostic testing for disease-susceptibility genes and lead to individually tailored treatment regimens for individuals with disease. Recent analyses (from both the public and private sector) suggest that the abundance of anticipated drug targets will dramatically increase pharmaceutical R&D costs. For example, it has been suggested that a threshold investment of $70-100 million will be required if companies are to profit from recent advances in bioinformatics. However, this investment may not yield a near-term return because current validation/development methods for drug targets are insufficiently robust to add value to R&D pipelines. Competitive considerations require companies to couple considerable infrastructure investment with cost-effective validation and/or development technology that has yet to be developed.

As described above, with advances in technology, the rational design and validation of new therapeutics increasingly will rely on the systematic interrogation of databases that contain genomic and proteomic information. One can imagine three pathways from database discovery to a validated product prototype, as shown in Figure C.2.

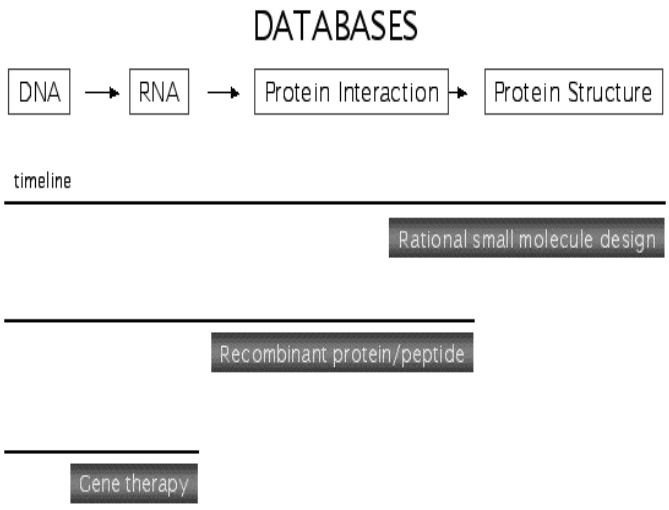

Figure C.2. Three pathways of drug discovery and development in the bioinformatics era.

For *Pathway 1, rational small-molecule design*, the methods for developing a small-molecule prototype are well established in the pharmaceutical industry, which reduces risk. However, it is not clear that small-molecule drugs can be designed, as shown above: the notion currently is without precedent (with perhaps the exception of inhibitors of HIV protease and influenza neuraminidase), and therefore is best considered as an unproven hypothesis.

A major advantage for *Pathway 2, recombinant protein/peptide design*, is that small-molecule prototypes need not be designed and validated at all, which may significantly accelerate product development. However, therapeutic peptides and recombinant proteins are generally ineffective when administered orally, and alternative routes of administration are generally associated with challenges in terms of formulation, compliance, efficacy, and safety.

A major advantage for *Pathway 3, gene therapy design*, is that one may proceed directly from database query to gene-based prototype — in theory, the shortest route to product validation and development. However, gene therapy is an early-stage technology, with known challenges in terms of efficacy and safety.

The Potential for Gene Therapy as a Validation / Delivery Platform

Gene therapy is the use of recombinant DNA as a biologic substance for therapeutic purposes (Bonadio 2000). Both viral and nonviral vectors have been employed. Nonviral vectors show many formulation and cost advantages, and they present a flexible chemistry. For example, the formulation of nonviral vectors with cationic agents results in nanometer-sized particles (synthetic polyplexes and lipoplexes) that show good efficiency (Felgner et al. 1997). Nonviral vectors have no theoretical sub-cloning limit, show a broad targeting specificity, transfect cells as episomes, and can be manufactured at scale relatively inexpensively. To enhance efficiency even further, one may use PEG to control surface properties of synthetic complexes, incorporate targeting moieties, use tissue-specific promoters, and incorporate fusogenic peptides and pH-responsive polymers.

On the other hand, the gain in gene-transfer efficiency associated with synthetic complexes must be balanced against the general lack of stability of polyplex and lipoplex vectors *in vivo* and the tendency of locally delivered cationic agents to cause tissue necrosis, which can be dramatic. Nonviral vectors are inefficient, and high doses may be required to achieve therapeutic effects. High-dose administration may be limited, however, by motifs in the vector backbone that stimulate the immune system (MacColl et al. 2001). While CpG-dependent immune stimulation is Th1-biased, SCID mice (Ballas, Rasmussen, and Krieg 1996) have shown increased levels of IFN- and IL-12 following plasmid-vector delivery (Klinman et al. 1996). Significantly, nonviral vector administration to animals has generated anti-DNA antibodies, leading to renal disease and premature death (Deng 1999). Relevant to the present application, Payette and colleagues (2001) recently showed that intramuscular delivery of a nonviral vector vaccine in mice led to destruction of antigen-expressing myocytes via a CTL-response.

Viruses are natural vectors for the transfer of recombinant DNA into cells. Recognition of this attribute has led to the design of engineered recombinant viral vectors for gene therapy. Viral vectors from retroviral, lentiviral, adenovirus, and herpes simplex species provide an important advantage in that they maximize gene

transfer efficiency (Kay, Glorioso, and Naldini 2001). Viral genomes consist of genes and *cis*-acting gene regulatory sequences. Although overlap exists, most *cis*-acting sequences map outside viral coding sequences, and this spatial segregation is exploited in the design of recombinant viral vectors. Additionally, coding sequences work in *trans,* and viral genomes can be expressed by heterologous plasmids or be incorporated in the chromatin of producer cells to ensure stability and limit remobilization. Therefore, to generate vector particles, therapeutic genes and *cis*-acting sequences are first subcloned into separate plasmids, which are introduced into the same cell. Transfected cells produce replication-defective particles able to transduce target cells.

Viral vectors have inherent properties that affect suitability for specific gene therapy applications. A useful property of retroviral vectors, for example, is the ability to integrate efficiently into the chromatin of target cells. Disruption of the nuclear membrane is absolutely required for the pre-integration complex to gain access to chromatin (Roe et al. 1993), and productive transduction by retroviral vectors is strictly dependent on target cell mitosis (Miller, Adam, and Miller 1990). (Integration does not, however, guarantee stable expression of the transduced gene.) Because only a small fraction of muscle fibers pass through mitosis at any given time, this effectively prevents the use of regulated retroviral vectors (Rando and Blau 1994) in direct *in vivo* muscle gene therapy.

In contrast, replication-defective Ad vectors are attractive because they transduce post-mitotic cells very efficiently *in vivo* (Kozarsky and Wilson 1993). However, Ad vectors induce toxic immune responses that abrogate gene expression (Yang et al. 1995; Somia and Verma 2000). In a relevant example, Rivera et al. (1999) studied the feasibility of regulated Ad gene delivery after intramuscular injection in mice. The investigators employed an Ad vector cocktail encoding human growth hormone (hGH) under the control of transcriptional-switch technology. In initial experiments using immune-deficient mice, a single IP injection of rapamycin (5.0-mg/kg) resulted in a 100-fold increase in the plasma hGH level. Levels then diminished to baseline over the next 14 days. Similar induction profiles were noted after five subsequent injections (administered periodically over 6 months), and a direct relationship was observed between the peak hGH level and the amount of rapamycin administered (the i.v. dose range was 0.01 to 0.25 mg/kg). However, in immune-competent animals, peak levels of hGH were 50-fold lower, and no induction was observed after the first administration of rapamycin. These results were attributed to the destructive cellular and humoral immune responses to the Ad vector.

Experience with gene therapy suggests that this technology could serve as a broad validation and delivery platform for Pathway 3. To succeed, however, gene therapy must become a technology that more closely conforms to the current framework for drug development by pharmaceutical companies. Toward this end, gene therapy will need to be more easily managed by physician and patient; capable of producing therapeutic protein in a precise, dose-responsive, controllable manner; and formulated in a more simple, stable, and inexpensive manner. Ideally, a controllable gene-delivery system should feature low baseline transgene expression, a high induction ratio, and tight control by a small molecule drug. Indeed, it is difficult to imagine any gene therapy (for any indication) that does not involve

regulated therapeutic gene expression as a way to avoid toxicity and still respond to the evolving nature of disease.

Among a multiplicity of DNA vector alternatives, recombinant adeno-associated viral (rAAV) vectors (Monahan and Samulski 2000) represent an attractive choice for a validation and delivery platform. rAAV vector particles efficiently transduce both dividing and nondividing cells, and the rAAV genome persists as integrated tandem repeats in chromosomal DNA. (Upon co-infection with a helper virus, AAV also transduces cells as an episome.) Elimination of AAV *rep* and *cap* coding sequences from rAAV prevents immune responses to viral gene products and the generation of wild-type helper virus (Hernandez et al. 1999; Xiao, Li, and Samulski 1996; Jooss et al. 1998). Transgene expression *in vivo* typically reaches a steady state after a gradual 2- to 10-week rise. Together, host chromosome integration and the absence of a cytotoxic T lymphocyte response provide a viable mechanism for long-term transgene expression, as demonstrated in the skeletal muscle (Herzog et al. 1999; Malik et al. 2000; Ye et al. 1999; Herzog et al. 1997) and brain (Davidson et al. 2000) of immunocompetent animals and in the skeletal muscle of human subjects (Kay et al. 2000). Importantly, the ability to conduct experiments is supported by the availability of small-scale procedures that allow the facile manufacture of sterile rAAV preparations at titers of 10^{11}-10^{12} vector genomes/mL (Auricchio et al. 2001). Even more importantly, rAAV gene therapy is controllable, as demonstrated below.

One promising technology (Figure C.3) employs a heterologous transcription factor that selectively binds the transgene promoter and activates transcription in response to a cell-permeant controller molecule (e.g., Rivera et al. 1996; Magari et al. 1997; Pollock et al. 2000). Activation is achieved by reconstitution of a transcription factor complex that couples independently expressed protein chimeras (Brown et al. 1994; Standaert et al. 1990). One protein consists of a unique DNA-binding domain called ZFHD1, genetically fused to FKBP. The other protein chimera consists of the activation domain of the p65 subunit of NFκB, fused with the rapamycin-binding domain of FRAP, which is termed FRB. Packaging limits of rAAV require that the three components of the system be incorporated into two vectors, one vector that expresses both transcription factors from a single transcriptional unit and a second vector containing the therapeutic gene driven by a

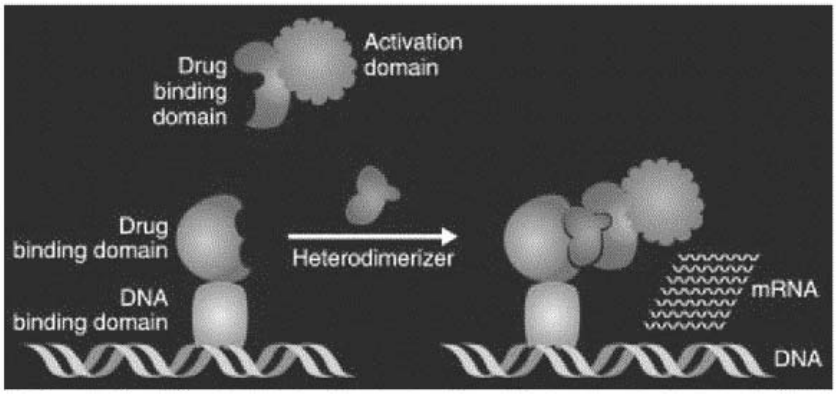

Figure C.3. Controlling gene expression using regulated transcription.

promoter recognized by the ZFHD1 DNA-binding domain. Infection of permissive human cells with equal quantities of the two AAV vectors at a high multiplicity of infection has resulted in full *in vitro* reconstitution of the regulated system with at least a 100-fold induction after exposure to rapamycin. (Effectiveness may be dramatically increased [Mateson et al. 1999] when chimeric transcriptional activators are expressed as noncovalent tetrameric bundles.)

The feasibility of reconstituting the regulated system *in vivo* has also been determined. Skeletal muscle has been selected for local delivery because muscle is permissive for rAAV transduction and because its component cells (muscle fibers) are long syncytia with extended nuclear domains that may be independently transduced with each vector. In one example (Ye et al. 1999), a controllable rAAV vector cocktail ($2x10^8$ infectious particles, with rAAV vectors at a 1:1 ratio) was injected into skeletal muscle of immune-competent mice. The administration of rapamycin resulted in 200-fold induction of erythropoietin in the plasma. Stable engraftment of this humanized system was achieved for six months, with similar results for at least three months in an immune-competent rhesus model.

The "transcriptional-switch" technology (described above) features an induction-decay response for the therapeutic protein that occurs on a time scale of days: transgene-encoded protein in blood typically peaks around 24 hours and then decreases to background over 4 to 14 days. This kinetic profile probably reflects the "early-point" of transgene regulation as well as the many potentially rate-limiting steps after therapeutic gene delivery. These steps involve the pharmacokinetics and pharmacodynamics of rapamycin (Mahalati and Kahan 2001) as well as the dynamic processes of transgene transcription, therapeutic protein translation and secretion, and therapeutic protein bioavailability. Such prolonged kinetics may be appropriate for certain proteins (e.g., erythropoietin) that govern relatively slow physiological

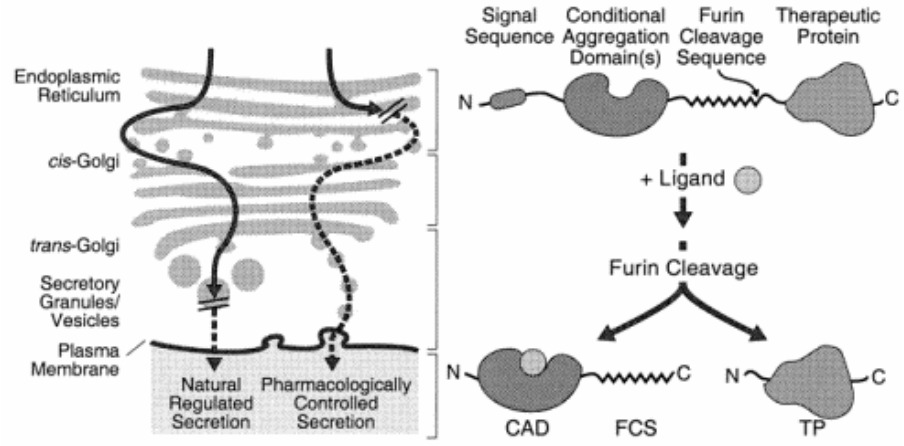

Figure C.4. Scheme for the pharmacologic control of protein secretion. (A) (*left*) Natural control of protein secretion (protein is stored in the secretory granules) is contrasted with the scheme for pharmacological control (protein is stored in the ER). (*right*) The therapeutic protein of interest (TP) is expressed as part of a fusion protein that contains, at its NH2-terminus, a signal sequence, a conditional aggregation domain (CAD), and a furin cleavage sequence (FCS). Processing and secretion of the TP is induced by ligand (Rivera et al. 2000).

processes. Prolonged kinetics may not be as appropriate, however, for proteins that regulate processes such as glucose homeostasis, which tend to be much faster.

To address this potential limitation of the transcriptional-switch system, Rivera et al. (2000), recently developed a second technology that allows protein secretion from the endoplasmic reticulum (ER) to be rapidly regulated Figure C.4). Therapeutic proteins are expressed as fusions with a conditional aggregation domain (CAD). CADs self-interact, and fusion proteins therefore form an aggregate in the ER that is far too large to be transported. Rivera and colleagues showed that the addition of cell-permeant ligand ("disaggregator") to transfected cells dissolves the aggregates and permits the rapid transport of therapeutic proteins from the ER via the constitutive secretory pathway.

To produce bioactive proteins, CAD moieties must be removed. Rivera et al. solved this problem by interposing a furin cleavage sequence between therapeutic protein and the CAD. In one example, Rivera et al. (2000) demonstrated that a natural version of hGH could be secreted in a controllable fashion using disaggregator technology. Thus, a single amino acid change (Phe^{36} to Met) converted monomeric FKBP12 into a CAD. Recombinant hGH was generated via a cDNA construct (Fig. C.3) consisting of a CMV promoter, signal sequence, four CAD motifs, a furin cleavage signal, and growth hormone (proinsulin was also used). Vectors were stably transfected into HT1080 cells, and fluorescence microscopy was used to demonstrate ER retention of both insulin and growth hormone in the absence of disaggregator. Cells expressing fusion proteins were then treated with increasing concentrations of disaggregator for two hours. The authors showed that accumulated protein was released by disaggregator administration, and the rate of release was controllable over an ~20-fold dose range. In the absence of ligand, fusion proteins were found only in cell lysate samples, whereas two hours after addition of ligand, fusion proteins were cleaved appropriately and secreted, as determined by Western analysis. Finally, myoblast transfer was used to demonstrate feasibility of the system in animal models. To this end, engineered cells were implanted into mice made diabetic by treatment with streptozotocin. Administration of vehicle failed to normalize serum glucose concentrations. However, after intravenous administration of ligand insulin was detected in serum within 15 minutes and peaked by 2 hours. Indeed, 2 hours after administration of a 10.0-mg/kg dose of ligand, the circulating insulin concentration increased to greater than 200.0-pM and serum glucose decreased concomitantly to normal. Lower doses of ligand were less effective.

Summary

Several trends have been identified:

a) Breakthroughs in controllable gene therapy technology have allowed therapeutic transgene expression to be regulated with precision over a period of months to years. The technology features low baseline transgene expression, a high induction ratio, and control via an orally available, cell permeant small molecule. Feasibility has been established in a series of elegant studies that employ recombinant adeno-associated viral (rAAV) vectors. *These breakthroughs are unique to gene therapy, i.e., similar levels of*

pro-drug stability and control simply do not exist for more traditional drug substances (small molecules, peptides, and proteins).

b) *One may see enormous improvements in patient care pathways.* For diabetes and other endocrinopathies, the standard of care may change from "multiple daily injections" to a "single injection of gene therapy followed by ingestion of multiple tablets each day." Drug therapy could truly be personalized: once individual disease patterns are established (e.g., via sensor technology), the patient and physician could work together to develop a rational, personalized regimen of small molecule administration that would be expected to yield improved compliance and better control of disease; this in turn should lessen the cost of disease to U.S. society.

c) Given the availability of a panel of cell-permeant small molecules, gene therapy becomes a combined validation/development platform in which the therapy is a stable pro-drug that remains controllable for years following initial injection of tissues such as skeletal muscle. The small molecule panel would likely form an important core element of a company's intellectual property.

d) Given the biological and technological complexity associated with genome analysis technology, an interdisciplinary spirit will be required to advance our knowledge base in basic science and drug development. Although significant technological hurdles must be traversed, the potential advantages are enormous if controllable gene therapy can realize its potential as a validation and delivery platform. Drug discovery and development may one day be routine (a more-or-less turnkey process), characterized by direct, efficient transitions *from* database query *to* rational isolation of the relevant cDNA *to* preclinical validation, *to* validation in human clinical trials (Fig. C.1). Because the "drug substance" typically will consist of a recombinant gene and a small-molecule controller, many aspects of formulation, manufacturing, biodistribution, and toxicity would be well understood *prior to* initiation of a new development program. Obviously, companies would operate in an environment of significantly reduced risk relative to the current situation; this environment would allow companies to explore a much broader range of drug targets than typically is explored today.

e) Finally, we envision a pharmaceutical industry that possesses the technological tools and economic incentives to take full advantage of the power of genomics. Specifically, the vision proposed here is that in 10 to 15 years the U.S. private sector will have a drug discovery/drug development pathway that is significantly more cost effective (more turnkey and less risky) than what we now have and is capable of taking full advantage of the promise of the human genome sequence. (Pharmaceutical companies could actually take calculated risks!) If this vision is realized, one can easily imagine how the process of technology transfer from the developed to the undeveloped world would be incentivized for the first time.

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IMPLICATIONS OF THE CONTINUUM OF BIOINFORMATICS

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The once impenetrable complexity of biology has come face to face with rapidly expanding microprocessing power and information management solutions, and this confluence is changing our world. The parallel development of tools needed to extract biological meaning from DNA, proteins, cells, tissues, organisms, and society as a whole has set the stage for improved understanding of biological mechanisms. This is being augmented by our ability to manage this information in uniform ways and to ask questions about relationships across broad levels of biological scale. This multiscalar description of biology from the molecular to the societal, with all of the tools needed to draw correlations across its landscape, is known as the continuum of bioinformatics (COB).

Though presently immature, the COB is growing in richness daily. Driven initially by the need to manage DNA and protein sequence data, it has grown with the inclusion of cellular imaging, tissue analysis, radiological imaging, and societal healthcare informatics inputs. It is presently virtual but, like the Internet before it, it is being tied together through the development of standard systems, query tools, and security measures. As it develops, the COB is changing our world through the enhancement of our understanding of biological process and the acceleration of development of products that can benefit man, animals, and plants. The unusual precision with which biological data is represented within the COB is making it possible to reduce the degrees of freedom normally accorded biological understanding — and therefore to enable the individualization of solutions that will protect life.

Nanotechnology will play a major role in the development of information gathering and processing systems for the COB.

Definition of Bioinformatics

The science of bioinformatics presents the rich complexity of biology in such a way that meaning can be extracted using digital tools. As a discipline having multiple parts, it can be defined overall in a number of ways. One definition of bioinformatics and its components is as follows (D'Trends n.d.):

(1) *Bioinformatics* - database-like activities involving persistent sets of data that are maintained in a consistent state over essentially indefinite periods of time

(2) *Computational biology* - the use of algorithmic tools to facilitate biological analyses

(3) *Bioinformation infrastructure* - the entire collective of information management systems, analysis tools and communication networks supporting biology

This composite definition points out the importance of three activities critical to the success of bioinformatics activities:

- The use of analytic methods to enable the presentation of biological information in digital fashion.
- The leveraging of massive digital storage systems and database technologies to manage the information obtained.
- The application of digital analytic tools to identify patterns in the data that clarify causes and effects in biological systems, augmented by visualization tools that enable the human mind to rapidly grasp these patterns.

Bioinformatics makes the complexity of biological systems tangible. Taken in the stepwise fashion described above, this complexity can often be reduced to terms that are understandable to scientists probing biological problems. Biological complexity is worthwhile to understand. A clear appreciation of cause and effect in biological systems can provide the knowledge needed to develop drugs and other medical therapies and also to provide a greater appreciation for what we are as humans beings. It is interesting to note that biological complexity is so extreme that it challenges the best that high-performance computing presently has to offer. Ironically, the fulfillment of the Socratic adage "Know Thyself" can now only be achieved through man's interaction with and dependence upon computing systems.

The recent accomplishment of sequencing the human genome (and now the genomes of several other species) focused attention on the information processing requirements at the molecular end of the biological spectrum. For a time, it seemed that "bioinformatics" was wholly concerned with the management and deciphering of genetic information. Soon, information descriptive of the patterns of expression of proteins and their interactions was added (proteomics). Since this information required stratification by disease type, cellular and tissue information became important to consider. Inevitably, it became apparent that information descriptive of the whole organism, such as radiological data, other morphometric data, chemistries, and other health record data should be included. Once this was done, aggregated societal data was the next logical addition.

The picture that has come into view is therefore one of a continuum of bioinformatics (Figure C.5). In the COB model, linked data at multiple scales of

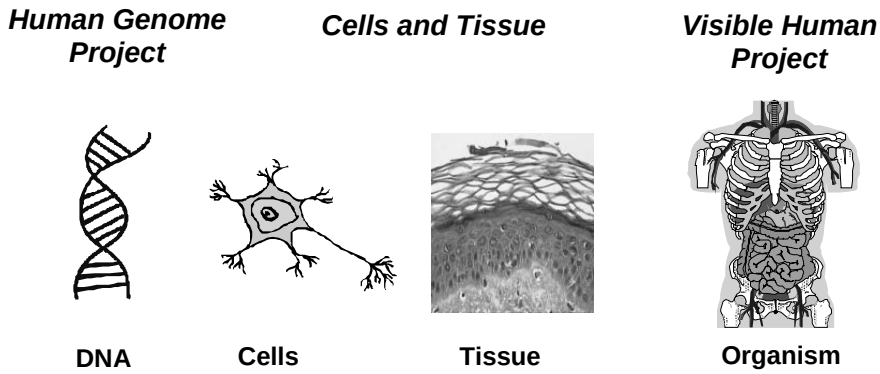

Figure C.5. Multiple scales of biological activity and form comprise the entire organism. The Continuum of Bioinformatics is an information system that includes and can correlate information from all of these scales of data. Though not shown in the figure, the aggregation of individual data into societal data (as in the form of healthcare statistics) is extremely valuable, since it places the individual's data within the context of the society as a whole.

biological complexity are considered together for both individuals and aggregates of individuals. The key to the value of the COB will be the ability to derive correlations between *causes* (such as gene expression, protein interactions, and the like) and *effects* (such as healthcare outcomes for individuals and societies). In this model, it may well be possible one day to determine the cost to society of the mutation of a single gene in a single individual! It will also be possible to predict with clarity which drugs will work for which individuals and why. By taking a reverse course through the COB from effects to causes, it will also be possible to sharply identify proteins that can serve as drug targets for specific disease states.

Information Capture

In order to benefit from the COB, information descriptive of biology at multiple scales must first be captured accurately and then managed such that different types of data can be interpreted with reference to one another. It is in this area that the convergence of nanotechnology and biotechnology will occur, since nanotechnology provides enabling mechanisms for the capture and management of complex biological information, particularly at the level of molecular expression data.

A simple way to look at this issue is to first note that to be useful in the COB context, all biological data must first be captured using techniques that enable its ultimate conversion to digital form. The mechanisms differ, depending upon the point in the COB under consideration. Table C.3 shows the levels of the COB and the tools needed to capture data digitally at the proper level of discretion to enable computerized correlation between data pools.

Table C.3
Tools required to capture human biological information at different levels of scale, constituting the Continuum Of Bioinformatics

Biological Scale	Tools For Information Capture
DNA, Genes	DNA Sequencers Electrophoresis Affinity Microarrays
Proteins	Electrophoresis Mass Spectrometry Affinity Microarrays
Cells	Bioassays Fluorescent probes Digital Imaging
Tissues	Digital Imaging Hyperquantitative Analysis
Organism	Digital Radiology (X-Ray, CT, MRI, PET) Chemistry Data Healthcare Record
Society	Aggregated Healthcare Records

Ideally, information at all levels of scale would be captured from the same individual and then aggregated into a societal record. Since this is impractical, aggregated information will most likely be used, and this will grow richer over time. Privacy concerns are often raised when highly discrete and potentially predictive personal information is gathered in this way. However, it is most likely that COB data (as this virtual network begins to merge together) will be anonymized sufficiently so that individuals will be protected. Indeed, one way to look at the COB is to envision it as a powerful reference database against which an individual's data can be compared in order to provide an individual with contextual information regarding his or her health at any point in time. This is the essence of what is known as "Systems Biology," as well.

Tissue Information as a Specific Instance

A specific example of the conversion of biological information to digital information occurs at the tissue level. Until recently, it was felt that only a pathologist could interpret the meaning of patterns of cells and other structural components of tissue. This meaning was summed up in the diagnosis that was applied to the tissue and used to guide healthcare decision-making. Over the past two decades, digital imaging of tissues on slides has created the basis for management of tissue information at the image level for ease of data sharing between pathologists and researchers. However, this did not convert the data completely into digital form, because human interpretation and diagnostic assignment of the overall image were still required. This limited the ability to correlate tissue data with other biological information to the level of resolution that diagnosis provided.

Recently, it has become possible to use automated machine vision analysis systems to measure all of the components that can be made visible within a tissue (both structural and functional) with reference to one another. This is known as *Hyperquantitative Analysis of Tissue* (Fig. C.6).

Preparation of tissue information in this way requires two steps:

a) automated imaging that enables location of tissue on a microscope slide and the capture of a composite image of the entire tissue — or tissues — on the slide

b) the application of image analytic software that has been designed to automatically segregate and co-localize in Cartesian space the visible components of tissue (including molecular probes, if applied)

Tissue information captured in this way enables very precise *mathematical comparison* of tissues to detect change (as in toxicology testing or, ultimately, clinical diagnostics). In each case, substantial work must first be done to collect normative reference data from tissue populations of interest.

More importantly, when tissue information is reduced to this level of scale, the data is made available for more precise *correlation* with other data sets in the continuum of bioinformatics in the following applications:

- *Backward correlation:* "Sorter" of genomic and proteomic data

  Rationale*:* When gene or protein expression data are culled from a tissue that has undergone hyperquantitative analysis, tighter correlations are possible between molecular expression patterns and tissue features whose known biological roles help to explain the mechanisms of disease — and therefore may help to identify drug targets more sharply.

- *Forward correlation:* Stratifier of diagnosis with respect to prognosis

  Rationale*:* When tissue information is collected along with highly detailed clinical descriptions and outcome data, subtle changes in tissue feature patterns within a diagnostic group may help to further stratify prognoses associated with

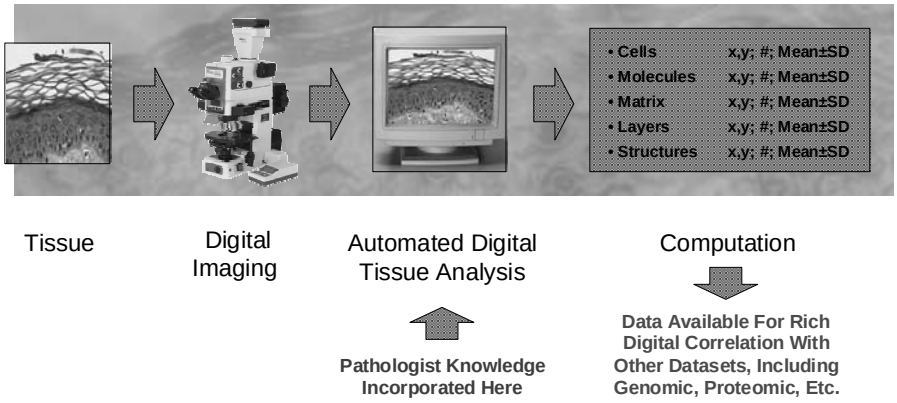

Figure C.6. Capture of tissue information in hyperquantitative fashion. All components of the tissue that can be made visible are located simultaneously after robotic capture of slide-based images. This step automates the analysis of tissue, putting it immediately into a form that enables sharing of images and derived data.

a diagnosis and may prompt more refined diagnostic classifications.

- *Pan Correlation:* Tighten linkage of prognosis with molecular diagnostics

  Rationale*:* Since tissue is the classical "site of diagnosis," the use of tissue information to correlate with molecular expression data and clinical outcome data validates those molecular expression patterns with reference to their associated diseases, enabling their confident application as molecular diagnostics.

Nanotechnology developments applicable to imaging and computational science will aid and abet these discoveries.

Information Management

The physical management of the large volumes of information needed to represent the COB is essentially an information storage and retrieval problem. Although only several years ago the amount of information that required management would have been a daunting problem, this is far less so today. Extremely large storage capacities in secure and fast computer systems are now commercially available. While excellent database systems are also available, none has yet been developed that completely meets the needs of the COB as envisioned. Database system development will continue to be required in order for the COB to be applied maximally. Several centers are now attempting the development of representative databases of this type.

Extracting Value From the Continuum of Bioinformatics

Once the COB is constructed and its anonymized data becomes available, it can be utilized by academia, industry, and government for multiple critical purposes. Table C.4 shows a short list of applications.

In order for COB data to be put to best use, considerable work will be needed to incorporate statistical methodology and robust graphical user interfaces into the COB. In some cases, the information gleaned will be so complex that new methods of visualization of data will need to be incorporated. The human mind is a powerful interpreter of graphical patterns. This may be the reason why tissue data — classically having its patterns interpreted visually by a pathologist — was the last in the continuum to be reduced to discrete digital form.

Table C.4
Applications of the COB in multiple sectors

Academic Applications	• Education • Research
Industrial Applications	• Drug Development • Medical Device Development • Tissue Engineering • Marketing
Government Applications	• Population Epidemiology • Disease Tracking • Healthcare Cost Management

As the COB develops, we are likely to see novel data visualization methods applied in ways that cannot be envisioned at all today. In each instance, the robustness of these tools will ultimately depend on the validity of the data that was entered into the COB and on the mode of application of statistical tools to the data being analyzed.

Impact on Human Health

The COB will significantly enhance our ability to put individual patterns of health and disease in context with that of the entire population. It will also enable us to better understand the mechanisms of disease, how disease extends throughout the population, and how it may be better treated. The availability of the COB will resect time and randomness from the process of scientific hypothesis testing, since data will be available in a preformed state to answer a limitless number of questions. Finally, the COB will enable the prediction of healthcare costs more accurately. All of these beneficial reesults will be accelerated through the application of nanotechnology principles and techniques to the creation and refinement of imaging, computational, and sensing technologies.

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SENSORY REPLACEMENT AND SENSORY SUBSTITUTION: OVERVIEW AND PROSPECTS FOR THE FUTURE

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The traditional way of dealing with blindness and deafness has been some form of sensory substitution — allowing a remaining sense to take over the functions lost as the result of the sensory impairment. With visual loss, hearing and touch naturally take over as much as they can, vision and touch do the same for hearing, and in the rare cases where both vision and hearing are absent (e.g., Keller 1908), touch provides the primary contact with the external world. However, because unaided sensory substitution is only partially effective, humans have long improvised with artifices to facilitate the substitution of one sense with another. For blind people, braille has served in the place of visible print, and the long cane has supplemented spatial hearing in the sensing of obstacles and local features of the environment. For deaf people, lip reading and sign language have substituted for the loss of speech reception. Finally, for people who are both deaf and blind, fingerspelling by the sender in the palm of the receiver (Jaffe 1994; Reed et al. 1990) and the Tadoma method of speech reception (involving placement of the receiver's hand over the speaker's face) have provided a means by which they can receive messages from others (Reed et al. 1992).

Assistive Technology and Sensory Substitution

Over the last several decades, a number of new assistive technologies, many based on electronics and computers, have been adopted as more effective ways of promoting sensory substitution. This is especially true for ameliorating blindness. For example, access to print and other forms of text has been improved with these technologies: electronic braille displays, vibtrotactile display of optically sensed print (Bliss et al. 1970), and speech display of text sensed by video camera (Kurzweil 1989). For obstacle avoidance and sensing of the local environment, a number of ultrasonic sensors have been developed that use either auditory or tactile displays (Brabyn 1985; Collins 1985; Kay 1985). For help with large-scale wayfinding, assistive technologies now include electronic signage, like the system of Talking Signs (Crandall et al. 1993; Loughborough 1979; see also http://www.talkingsigns.com/), and navigation systems relying on the Global Positioning System (Loomis et al. 2001), both of which make use of auditory displays. For deaf people, improved access to spoken language has been made possible by automatic speech recognition coupled with visible display of text; in addition, research has been conducted on vibrotactile speech displays (Weisenberger et al. 1989) and synthetic visual displays of sign language (Pavel et al. 1987). Finally, for deaf-blind people, exploratory research has been conducted with electromechanical Tadoma displays (Tan et al. 1989) and finger spelling displays (Jaffe 1994).

Interdisciplinary Nature of Research on Sensory Replacement / Sensory Substitution

This paper is concerned with compensating for the loss of vision and hearing by way of sensory replacement and sensory substitution, with a primary focus on the latter. Figure C.7 shows the stages of processing from stimulus to perception for vision, hearing, and touch (which often plays a role in substitution) and indicates the

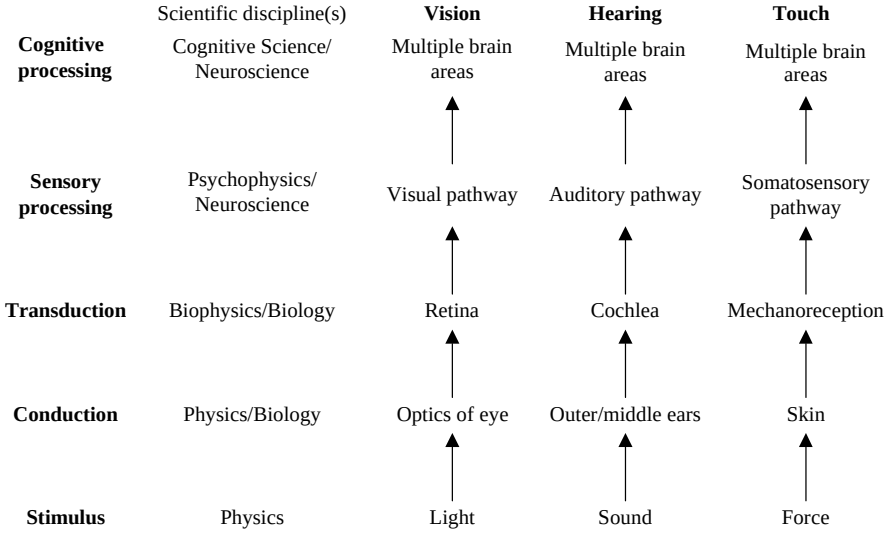

Figure C.7. Sensory modalities and related disciplines.

associated basic sciences involved in understanding these stages of processing. (The sense of touch, or haptic sense, actually comprises two submodalities: kinesthesis and the cutaneous sense [Loomis and Lederman 1986]; here we focus on mechanical stimulation). What is clear is the extremely interdisciplinary nature of research to understand the human senses. Not surprisingly, the various attempts to use high technology to remedy visual and auditory impairments over the years have reflected the current scientific understanding of these senses at the time. Thus, there has been a general progression of technological solutions starting at the distal stages (front ends) of the two modalities, which were initially better understood, to solutions demanding an understanding of the brain and its functional characteristics, as provided by neuroscience and cognitive science.

Sensory Correction and Replacement

In certain cases of sensory loss, sensory correction and replacement are alternatives to sensory substitution. Sensory correction is a way to remedy sensory loss prior to transduction, the stage at which light or sound is converted into neural activity (Figure C.7). Optical correction, such as eyeglasses and contact lenses, and surgical correction, such as radial keratotomy (RK) and laser in situ keratomileusis (LASIK), have been employed over the years to correct for refractive errors in the optical media prior to the retina. For more serious deformations of the optical media, surgery has been used to restore vision (Valvo 1971). Likewise, hearing aids have long been used to correct for conductive inefficiencies prior to the cochlea. Because our interest is in more serious forms of sensory loss that cannot be overcome with such corrective measures, the remainder of this section will focus on sensory replacement using bionic devices.

In the case of deafness, tremendous progress has already been made with the cochlear implant, which involves replacing much of the function of the cochlea with direct electrical stimulation of the auditory nerve (Niparko 2000; Waltzman and Cohen 2000). In the case of blindness, there are two primary approaches to remedying blindness due to sensorineural loss: retinal and cortical prostheses. A retinal prosthesis involves electrically stimulating retinal neurons beyond the receptor layer with signals from a video camera (e.g., Humayun and de Juan 1998); it is feasible when the visual pathway beyond the receptors is intact. A cortical prosthesis involves direct stimulation of visual cortex with input driven by a video camera (e.g., Normann 1995). Both types of prosthesis present enormous technical challenges in terms of implanting the stimulator array, power delivery, avoidance of infection, and maintaining long-term effectiveness of the stimulator array.

There are two primary advantages of retinal implants over cortical implants. The first is that in retinal implants, the sensor array will move about within the mobile eye, thus maintaining the normal relationship between visual sensing and eye movements, as regulated by the eye muscle control system. The second is that in retinal implants, connectivity with the multiple projection centers of the brain, like primary visual cortex and superior colliculus, is maintained without the need for implants at multiple sites. Cortical implants, on the other hand, are technically more feasible (like the delivery of electrical power), and are the only form of treatment for blindness due to functional losses distal to visual cortex. For a discussion of other pros and cons of retinal and cortical prostheses, visit the Web site

(http://insight.med.utah.edu/research/normann/normann.htm) of Professor Richard Normann of the University of Utah.

Interplay of Science and Technology

Besides benefiting the lives of blind and deaf people, information technology in the service of sensory replacement and sensory substitution will continue to play another very important role — contributing to our understanding of sensory and perceptual function. Because sensory replacement and sensory substitution involve modified delivery of visual and auditory information to the perceptual processes in the brain, the way in which perception is affected or unaffected by such modifications in delivery is informative about the sensory and brain processes involved in perception. For example, the success or lack thereof of using visual displays to convey the information in the acoustic speech signal provides important clues about which stages of processing are most critical to effective speech reception. Of course, the benefits flow in the opposite direction as well: as scientists learn more about the sensory and brain processes involved in perception, they can then use the knowledge gained to develop more effective forms of sensory replacement and substitution.

Sensory Replacement and the Need for Understanding Sensory Function

To the layperson, sensory replacement might seem conceptually straightforward — just take an electronic sensor (e.g., microphone or video camera) and then use its amplified signal to drive an array of neurons somewhere within the appropriate sensory pathway. This simplistic conception of "sensory organ replacement" fails to recognize the complexity of processing that takes place at the many stages of processing in the sensory pathway. Take the case of hearing. Replacing an inoperative cochlea involves a lot more than taking the amplified signal from a microphone and using it to stimulate a collection of auditory nerve fibers. The cochlea is a complex transducer that plays sound out in terms of frequency along the length of the cochlea. Thus, the electronic device that replaces the inoperative cochlea must duplicate its sensory function. In particular, the device needs to perform a running spectral analysis of the incoming acoustic signal and then use the intensity and phase in the various frequency channels to drive the appropriate auditory nerve fibers. This one example shows how designing an effective sensory replacement begs detailed knowledge about the underlying sensory processes. The same goes for cortical implants for blind people. Simply driving a large collection of neurons in primary visual cortex by signals from a video camera after a simple spatial sorting to preserve retinotopy overlooks the preprocessing of the photoreceptor signals being performed by the intervening synaptic levels in the visual pathway. The most effective cortical implant will be one that stimulates the visual cortex in ways that reflect the normal preprocessing performed up to that level, such as adaptation to the prevailing illumination level.

Sensory Substitution: An Analytic Approach

If sensory replacement seems conceptually daunting, it pales in comparison with sensory substitution. With sensory substitution, the goal is to substitute one sensory modality that is impaired or nonfunctioning with another intact modality (Bach-y-Rita 1972). It offers several advantages over sensory replacement: (1) Sensory

substitution is suitable even for patients suffering sensory loss because of cortical damage; and (2) because the interface with the substituting modality involves normal sensory stimulation, there are no problems associated with implanting electrodes. However, because the three spatial modalities of vision, hearing, and touch differ greatly in terms of their processing characteristics, the hope that one modality, aided by some single device, can simply assume all of the functions of another is untenable. Instead, a more reasonable expectation is that one modality can only substitute for another in performance of certain limited functions (e.g., reading of print, obstacle avoidance, speech reception). Indeed, research and development in the field of sensory substitution has largely proceeded with the idea of restoring specific functions rather than attempting to achieve wholesale substitution. A partial listing follows of the functions performed by vision and hearing, which are potential goals for sensory substitution:

- **Some functions of vision = potential goals for sensory substitution**
  - access to text (e.g., books, recipes, assembly instructions, etc.)
  - access to static graphs/pictures
  - access to dynamic graphs/pictures (e.g., animations, scientific visualization)
  - access to environmental information (e.g., business establishments and their locations)
  - obstacle avoidance
  - navigation to remote locations
  - controlling dynamic events in 3-D (e.g., driving, sports)
  - access to social signals (e.g., facial expressions, eye gaze, body gestures)
  - visual aesthetics (e.g., sunset, beauty of a face, visual art)
- **Some functions of audition = potential goals for sensory substitution**
  - access to signals and alarms (e.g., ringing phone, fire alarm)
  - access to natural sounds of the environment
  - access to denotative content of speech
  - access to expressive content of speech
  - aesthetic response to music

An analytic approach to using one sensory modality (henceforth, the "receiving modality") to take over a function normally performed by another is to (1) identify what optical, acoustic, or other information (henceforth, the "source information") is most effective in enabling that function and (2) to determine how to transform the source information into sensory signals that are effectively coupled to the receiving modality.

The first step requires research to identify the source information necessary to perform a function or range of functions. Take, for example, the function of obstacle avoidance. A person walking through a cluttered environment is able to avoid bumping into obstacles, usually by using vision under sufficient lighting. Precisely what visual information or other form of information (e.g., ultrasonic, radar) best

affords obstacle avoidance? Once one has identified the best information to use, one is then in a position to address the second step.

Sensory Substitution: Coupling the Required Information to the Receiving Modality

Coupling the source information to the receiving modality actually involves two different issues: sensory bandwidth and the specificity of higher-level representation. After research has determined the information needed to perform a task, it must be determined whether the sensory bandwidth of the receiving modality is adequate to receive this information. Consider the idea of using the tactile sense to substitute for vision in the control of locomotion, such as driving. Physiological and psychophysical research reveals that the sensory bandwidth of vision is much greater than the bandwidth of the tactile sense for any circumscribed region of the skin (Loomis and Lederman 1986). Thus, regardless of how optical information is transformed for display onto the skin, it seems unlikely that the bandwidth of tactile processing is adequate to allow touch to substitute for this particular function. In contrast, other simpler functions, such as detecting the presence of a bright flashing alarm signal, can be feasibly accomplished using tactile substitution of vision.

Even if the receiving modality has adequate sensory bandwidth to accommodate the source information, this is no guarantee that sensory substitution will be successful, because the higher-level processes of vision, hearing, and touch are highly specialized for the information that typically comes through those modalities. A nice example of this is the difficulty of using vision to substitute for hearing in deaf people. Even though vision has greater sensory bandwidth than hearing, there is yet no successful way of using vision to substitute for hearing in the reception of the raw acoustic signal (in contrast to sign language, which involves the production of visual symbols by the speaker). Evidence of this is the enormous challenge in deciphering an utterance represented by a speech spectrogram. There is the celebrated case of Victor Zue, an engineering professor who is able to translate visual speech spectrograms into their linguistic descriptions. Although his skill is an impressive accomplishment, the important point here is that enormous effort is required to learn this skill, and decoding a spectrogram of a short utterance is very time-consuming. Thus, the difficulty of visually interpreting the acoustic speech signal suggests that presenting an isomorphic representation of the acoustic speech signal does not engage the visual system in a way that facilitates speech processing.

Presumably there are specialized mechanisms in the brain for extracting the invariant aspects of the acoustic signal; these invariant aspects are probably articulatory features, which bear a closer correspondence with the intended message. Evidence for this view is the relative success of the Tadoma method of speech reception (Reed et al. 1992). Some deaf-blind individuals are able to receive spoken utterances at nearly normal speech rates by placing a hand on the speaker's face. This direct contact with articulatory features is presumably what allows the sense of touch to substitute more effectively than visual reception of an isomorphic representation of the speech signal, despite the fact that touch has less sensory bandwidth than vision (Reed et al. 1992).

Although we now understand a great deal about the sensory processing of visual, auditory, and haptic perception, we still have much to learn about the

perceptual/cognitive representations of the external world created by each of these senses and the cortical mechanisms that underlie these representations. Research in cognitive science and neuroscience will produce major advances in the understanding of these topics in the near future. Even now, we can identify some important research themes that are relevant to the issue of coupling information normally sensed by the impaired modality with the processing characteristics of the receiving modality.

Achieving Sensory Substitution Through Abstract Meaning

Prior to the widespread availability of digital computers, the primary approach to sensory substitution using electronic devices was to use analog hardware to map optical or acoustic information into one or isomorphic dimensions of the receiving modality (e.g., using video to sense print or other high contrast 2-D images and then displaying isomorphic tactile images onto the skin surface). The advent of the digital computer has changed all this, for it allows a great deal of signal processing of the source information prior to its display to the receiving modality. There is no longer the requirement that the displayed information be isomorphic to the information being sensed. Taken to the extreme, the computer can use artificial intelligence algorithms to extract the "meaning" of the optical, acoustic, or other information needed for performance of the desired function and then display this meaning by way of speech or abstract symbols.

One of the great success stories in sensory substitution is the development of text-to-speech devices for the visually impaired (Kurzweil 1989). Here, printed text is converted by optical character recognition into electronic text, which is then displayed to the user as synthesized speech. In a similar vein, automatic speech recognition and the visual display of text may someday provide deaf people with immediate access to the speech of any desired interactant. One can also imagine that artificial intelligence may someday provide visually impaired people with detailed verbal descriptions of objects and their layout in the surrounding environment. However, because inculcating such intelligence into machines has proven far more challenging than was imagined several decades ago, exploiting the intelligence of human users in the interpretation of sensory information will continue to be an important approach to sensory substitution. The remaining research themes deal with this more common approach.

Amodal Representations

For 3-D space perception (e.g., perception of distance) and spatial cognition (e.g., large-scale navigation), it is quite likely that vision, hearing, and touch all feed into a common area of the brain, like the parietal cortex, with the result that the perceptual representations created by these three modalities give rise to amodal representations. Thus, seeing an object, hearing it, or feeling it with a stick, may all result in the same abstract spatial representation of its location, provided that its perceived location is the same for the three senses. Once an amodal representation has been created, it then might be used to guide action or cognition in a manner that is independent of the sensory modality that gave rise to it (Loomis et al. 2002). To the extent that two sensory modalities do result in shared amodal representations, there is immediate potential for one modality substituting for the other with respect to functions that rely on the amodal representations. Indeed, as mentioned at the outset

of this chapter, natural sensory substitution (using touch to find objects when vision is impaired) exploits this very fact. Clearly, however, an amodal representation of spatial layout derived from hearing may lack the detail and precision of one derived from vision because the initial perceptual representations differ in the same way as they do in natural sensory substitution.

Intermodal Equivalence: Isomorphic Perceptual Representations

Another natural basis for sensory substitution is isomorphism of the perceptual representations created by two senses. Under a range of conditions, visual and haptic perception result in nearly isomorphic perceptual representations of 2-D and 3-D shapes (Klatzky et al. 1993; Lakatos and Marks 1999; Loomis 1990; Loomis et al. 1991). The similar perceptual representations are probably the basis both for cross-modal integration, where two senses cooperate in sensing spatial features of an object (Ernst et al. 2001; Ernst and Banks 2002; Heller et al. 1999), and for the ease with which subjects can perform cross-modal matching, that is, feeling an object and then recognizing it visually (Abravanel 1971; Davidson et al. 1974). However, there are interesting differences between the visual and haptic representations of objects (e.g., Newell et al. 2001), differences that probably limit the degree of cross-modal transfer and integration. Although the literature on cross-modal integration and transfer involving vision, hearing, and touch goes back years, this is a topic that is receiving renewed attention (some key references: Ernst and Banks 2002; Driver and Spence 1999; Heller et al. 1999; Martino and Marks 2000; Massaro and Cohen 2000; Welch and Warren 1980).

Synesthesia

For a few rare individuals, synesthesia is a strong correlation between perceptual dimensions or features in one sensory modality with perceptual dimensions or features in another (Harrison and Baron-Cohen 1997; Martino and Marks 2001). For example, such an individual may imagine certain colors when hearing certain pitches, may see different letters as different colors, or may associate tactile textures with voices. Strong synesthesia in a few rare individuals cannot be the basis for sensory substitution; however, much milder forms in the larger population, indicating reliable associations between intermodal dimensions that may be the basis for cross-modal transfer (Martino and Marks 2000), might be exploited to produce more compatible mappings between the impaired and substiting modalities. For example, Meijer (1992) has developed a device that uses hearing to substitute for vision. Because the natural correspondence between pitch and elevation is space (e.g., high-pitched tones are associated with higher elevation), the device uses the pitch of a pure tone to represent the vertical dimension of a graph or picture. The horizontal dimension of a graph or picture is represented by time. Thus, a graph portraying a 45º diagonal straight line is experienced as a tone of increasing pitch as a function of time. Apparently, this device is successful for conveying simple 2-D patterns and graphs. However, it would seem that images of complex natural scenes would result in a cacophony of sound that would be difficult to interpret.

Multimodal Sensory Substitution

The discussion of sensory substitution so far has assumed that the source information needed to perform a function or functions is displayed to a single receiving modality, but clearly there may be value in using multiple receiving

modalities. A nice example is the idea of using speech and audible signals together with force feedback and vibrotactile stimulation from a haptic mouse to allow visually impaired people to access information about 2-D graphs, maps, and pictures (Golledge 2002, this volume). Another aid for visually impaired people is the "Talking Signs" system of electronic signage (Crandall et al. 1993), which includes transmitters located at points of interest in the environment that transmit infrared signals carrying speech information about the points of interest. The user holds a small receiver in the hand that receives the infrared signal when pointed in the direction of the transmitter; the receiver then displays the speech utterance by means of a speaker or earphone. In order to localize the transmitter, the user rotates the receiver in the hand until receiving the maximum signal strength; thus, haptic information is used to orient toward the transmitter, and speech information conveys the identity of the point of interest.

Rote Learning Through Extensive Exposure

Even when there is neither the possibility of extracting meaning using artificial intelligence algorithms nor the possibility of mapping the source information in a natural way onto the receiving modality, effective sensory substitution is not completely ruled out. Because human beings, especially when they are young, have a large capacity for learning complex skills, there is always the possibility that they can learn mappings between two sensory modalities that differ greatly in their higher-level interpretative mechanisms (e.g., use of vision to apprehend complex auditory signals or of hearing to apprehend complex 2-D spatial images). As mentioned earlier, Meijer (1992) has developed a device (The vOICe) that converts 2-D spatial images into time-varying auditory signals. While based on the natural correspondence between pitch and height in a 2-D figure, it seems unlikely that the higher-level interpretive mechanisms of hearing are suited to handling complex 2-D spatial images usually associated with vision. Still, it is possible that if such a device were used by a blind person from very early in life, the person might develop the equivalent of rudimentary vision. On the other hand, the previously discussed example of the difficulty of visually interpreting speech spectrograms is a good reason not to base one's hope too much on this capacity for learning.

Brain Mechanisms Underlying Sensory Substitution and Cross-Modal Transfer

In connection with his seminal work with the Tactile Vision Substitution System, which used a video camera to drive an electrotactile display, Bach-y-Rita (1967, 1972) speculated that the functional substitution of vision by touch actually involved a reorganization of the brain, whereby the incoming somatosensory input came to be linked to and analyzed by visual cortical areas. Though a radical idea at the time, it has recently received confirmation by a variety of studies involving brain imaging and transcranial magnetic stimulation (TMS). For example, research has shown that (1) the visual cortex of skilled blind readers of braille is activated when they are reading braille (Sadata et al. 1996), (2) TMS delivered to the visual cortex can interfere with the perception of braille in similar subjects (Cohen et al. 1997), and (3) that the visual signals of American Sign Language activate the speech areas of deaf subjects (Neville et al. 1998).

Future Prospects for Sensory Replacement and Sensory Substitution

With the enormous increases in computing power, the miniaturization of electronic devices (nanotechnology), the improvement of techniques for interfacing electronic devices with biological tissue, and increased understanding of the sensory pathways, the prospects are great for significant advances in sensory replacement in the coming years. Similarly, there is reason for great optimism in the area of sensory substitution. As we come to understand the higher level functioning of the brain through cognitive science and neuroscience research, we will know better how to map source information into the remaining intact senses. Perhaps even more important will be breakthroughs in technology and artificial intelligence. For example, the emergence of new sensing technologies, as yet unknown, just as the Global Positioning System was unknown several decades ago, will undoubtedly provide blind and deaf people with access to new types of information about the world around them. Also, the increasing power of computers and increasing sophistication of artificial intelligence software will mean that computers will be increasingly able to use this sensed information to build representations of the environment, which in turn can be used to inform and guide visually impaired people using synthesized speech and spatial displays. Similarly, improved speech recognition and speech understanding will eventually provide deaf people better communication with others who speak the same or even different languages. Ultimately, sensory replacement and sensory substitution may permit people with sensory impairments to perform many activities that are unimaginable today and to enjoy a wide range of experiences that they are currently denied.

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VISION STATEMENT: INTERACTING BRAIN

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Brain functional studies are currently performed by several instruments, most having limitations at this time. PET and SPECT use have labeled glucose as an indicator of metabolic activity; however, they may not be used within a short time interval and also can be expensive. MRI is a versatile brain imaging technique, but is highly unlikely to be "wearable." MEG is an interesting technology to measure axon-derived currents with a high accuracy at a reasonable speed; this still requires minimal external magnetic fields, and a triply shielded micro-metal cage is required for the entire subject. While thermography has some advantages, the penetration is very small, and the presence of overlying tissues is a great problem. Many brain responses during cognitive activities may be recognized in terms of changes in blood volume and oxygen saturation at the brain part responsible. Since hemoglobin is a natural and strong optical absorber, changes in this molecule can be monitored by the near infrared (NIR) detection method very effectively without applying external contrast agents (Chance, Kang, and Sevick 1993). NIR can monitor not only the blood volume changes (the variable that most of the currently used methods are measuring) but also hemoglobin saturation (the variable that provides the actual energy usage) (Chance, Kang, and Sevick 1993;Hoshe et al. 1994; Chance et al

1998). Among the several brain imagers, the "NIR Cognoscope" (Figure C.8) is one of a few that have wearability (Chance et al. 1993; Luo, nioka, and Chance 1996; Chance et al 1998). Also, with fluorescent-labeled neuroreceptors or metabolites (such as glucose), the optical method will have a similar capability for such metabolic activities as PET and SPECT (Kang et al. 1998).

Nanotechnology and information technology (IT) can be invaluable for the development of future optical cognitive instruments. Nano-biomarkers targeted for cerebral function representing biomolecules will enable us to pinpoint the areas responsible for various cognitive activities as well as to diagnose various brain disorders. Nano-sized sources and detectors operated by very long lasting nano-sized batteries will be also very useful for unobstructed studies of brain function. It is important to acknowledge that in the process of taking cognitive function measurements, the instrument itself or the person who conducts the measurements should not (or should minimally) interfere with or distract the subject's cognitive activities. The ultimate optical system for cognitive studies, therefore, requires wireless instrumentation.

It is envisioned that once nanotech and IT are fully incorporated into the optical instrumentation, the sensing unit will be very lightweight, disposable Band-aid™ sensor/detector applicators or hats (or helmets) having no external connection. Stimuli triggering various cognitive activities can be given through a computer screen or visor with incorporating a virtual reality environment. Signal acquisition will be accomplished by telemetry and will be analyzed in real time. The needed feedback stimulus can also be created, depending on the nature of the analysis needed for further tests or treatments. Some of the important future applications of the kind of "cognoscope" described above are as follows:

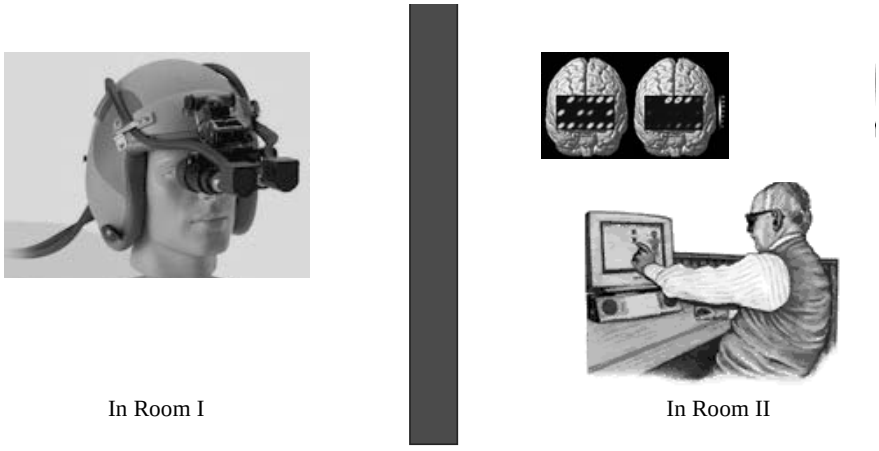

Figure C.8. A schematic diagram of the future NIR Cognosope. (a) A wireless, hat-like multiple source-detector system can be used for brain activities while the stimulus can be given though a visor-like interactive device. While a subject can be examined (or tested) in a room (room I) without any disturbance by examiners or other non-cognitive stimuli, the examiner can obtain the cognitive response through wireless transmission, can analyze the data in real-time, and also may be able to additional stimuli to the subjects for further tests, in another room (room II).

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2. Identification of children with learning disabilities (Chance et al. 1993; Hoshe et al. 1994; Chance et al. 1998)
3. Assessment of effectiveness in teaching techniques (Chance et al. 1993; Hoshe et al. 1994; Heekeren et al. 1997; Chance et al. 1998)
4. Applications for cognitive science — study of the thinking process (Chance et al. 1993; Hoshe et al. 1994; Chance et al. 1998)
5. Localization of brain sites responding to various stimuli (Gratton et al. 1995; Luo, Nioka, and Chance 19997; Heekeren et al. 1997; Villringer and Chance 1997)
6. Identification of the emotional state of a human being
7. Communicating with others without going through currently used sensory systems

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FOCUSING THE POSSIBILITIES OF NANOTECHNOLOGY FOR COGNITIVE EVOLUTION AND HUMAN PERFORMANCE

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Two statements are advanced in this paper:

1. Nanotechnology can help drive our cognitive evolution.
2. Nanotechnology applications can help us monitor distractibility and critical judgment, allowing unprecedented improvements in human performance.

The following will provide supporting arguments for these two positions, one general and one specific, regarding applications of nanotechnology for human performance. This vision and its transforming strategy will require the convergence of nanoscience, biotechnology, advanced computing, and principles in cognitive neuroscience.

Our Cognitive Evolution

How did the human brain acquire its incomparable power? Our species emerged less than 200,000 years ago, but it has no "new" modules compared to other primates. Our brains have retained vestiges from our evolutionary ancestors. The vertebrate (e.g., fish) nervous system is very old, and we have retained elements of the vertebrate brain, especially in the organization of spinal cord and brainstem systems. One radical change in evolution occurred in the transition from the aquatic to terrestrial environment. New "modules" arose to deal with the more complex needs of this environment in the form of the thalamic, basal ganglia, and cortical "modules" evident in the mammalian brain. The changes in brain structure between lower and higher mammals are related to size rather than to any novel structures. There was a dramatic growth in the size of the cerebral cortex between higher mammals and monkeys. But the difference between the monkey brain, the ape brain, and the human brain is again one of size. In comparing these three brains, we find that the size of the primary cortical areas (those dealing with sensory and motor functions) are similar in size, but in higher species, secondary and especially tertiary cortical areas (those dealing with higher-level processing of sensory and motor information) are the ones undergoing dramatic increases in size, especially in the human. That is, we have conserved a number of brain structures throughout evolution, but we seem to just have more of everything, especially cortex (Donald 1991).

In individuals, the factors that determine the anatomy of our cortex are genes, environment, and enculturation (Donald 1991). For instance, the structure of the basic computational unit of the cortex, the cortical column, is set genetically. However, the connectivity between cortical columns, which brings great computational power based on experience, is set by the environment, especially during critical stages in development. Moreover, the process of enculturation determines the plastic anatomical changes that allow entire circuits to be engaged in everyday human performance. This can be demonstrated experimentally. Genetic mutations lead to dramatic deficits in function; but if there is no genetic problem yet environmental exposure is prevented (such as covering the eyes during a critical period in development), lifelong deficits (blindness) result. If both genetic and

environmental factors proceed normally but enculturation is withdrawn, symbolic skills and language fail to develop, with drastic effects.

The unprecedented growth of the cortex exposed to culture allowed us to develop more complex skills, language, and unmatched human performance. It is thought that it is our capacity to acquire symbolic skills that has led to our higher intelligence. Once we added symbols, alphabets, and mathematics, biological memory became inadequate for storing our collective knowledge. That is, the human mind became a "hybrid" structure built from vestiges of earlier biological stages, new evolutionarily-driven modules, and external (cultural "peripherals") symbolic memory devices (books, computers, etc.), which, in turn, have altered its organization, the way we "think" (Donald 1991). That is, just as we use our brain power to continue to develop technology, that technological enculturation has an impact on the way we process information, on the way our brain is shaped. This implies that we are more complex than any creatures before, and that we may not have yet reached our final evolutionary form. Since we are still evolving, the inescapable conclusion is that nanotechnology can help drive our evolution. This should be the charge to our nanoscientists: Develop nanoscale hybrid technology.

What kind of hybird structures should we develop? It is tempting to focus nanotechnology research on brain-machine integration, to develop *implantable* devices (rather than *peripheral* devices) to "optimize" detection, perception, and responsiveness, or to increase "computational power" or memory storage. If we can ever hope to do this, we need to know how the brain processes information. Recent progress in information processing in the brain sciences, in a sense, parallels that of advances in computation. According to Moore's Law, advances in hardware development enable a doubling of computing and storage power every 18 months, but this has not led to similar advances in software development, as faster computers seem to encourage less efficient software (Pollack 2002, this volume). Similarly, brain research has given us a wealth of information on the hardware of the brain, its anatomical connectivity and synaptic interactions, but this explosion of information has revealed little about the software the brain uses to process information and direct voluntary movement. Moreover, there is reason to believe that we tailor our software, developing more efficient "lines of code" as we grow and interact with the environment and culture. In neurobiological terms, the architecture of the brain is determined genetically, the connectivity pattern is set by experience, and we undergo plastic changes throughout our lives in the process of enculturation. Therefore, we need to hone our skills on the software of the brain.

What kind of software does the brain use? The brain does not work like a computer; it is not a digital device; it is an analog device. The majority of computations in the brain are performed in analog format, in the form of graded receptor and synaptic potentials, not all-or-none action potentials that, after all, end up inducing other grade potentials. Even groups of neurons, entire modules, and multi-module systems all generate waveforms of activity, from the 40 Hz rhythm thought to underlie binding of sensory events to slow potentials that may underlie long-term processes. Before we can ever hope to implant or drive machines at the macro, micro, or nano scale, the sciences of information technology and advanced computing need to sharpen our skills at analog computing. This should be the charge to our information technology colleagues: Develop analog computational software.

However, we do not have to wait until we make breakthroughs in that direction, because we can go ahead and develop nanoscale *peripherals* in the meantime.

Improving Human Performance

Sensory Gating

Human performance, being under direct control from the brain, is dependent on a pyramid of processes. Accurate human performance depends on practice gained from learning and memory, which in turn depend on selective attention to the performance of the task at hand, which in turn depends on "preattentional" arousal mechanisms that determine a level of attention (e.g., I need to be awake in order to pay attention). Human performance can be improved with training, which involves higher-level processes such as learning and memory. However, the most common factor leading to poor human performance is a lower-level process, lack of attention, or distractibility. Distractibility can result from fatigue, stress, and disease, to name a few. Is it possible to decrease the degree of distractibility, or at least to monitor the level of distractibility? Can nanotechnology provide a critical service in the crucial area of distractibility?

The National Research Council's Committee on Space Biology and Medicine (1998) has concluded,

> Cumulative stress has certain reliable effects, including psychophysiological changes related to alterations in the sympathetic-adrenal-medullary system and the hypothalamic-pituitary-adrenal axis (hormonal secretions, muscle tension, heart and respiration rate, gastrointestinal symptoms), subjective discomfort (anxiety; depression; changes in sleeping, eating and hygiene), interpersonal friction, and impairment of sustained cognitive functioning. *The person's appraisal of a feature of the environment as stressful and the extent to which he or she can cope with it are often more important than the objective characteristics of the threat*.

It is therefore critical to develop a *method for measuring our susceptibility under stress to respond inappropriately to features of the environment*. "Sensory gating" has been conceptualized as a critical function of the central nervous system to filter out extraneous background information and to focus attention on newer, more salient stimuli. By monitoring our sensory gating capability, our ability to appraise and filter out unwanted stimuli can be assessed, and the chances of successful *subsequent* task performance can be determined.

One proposed measure of sensory gating capability is the P50 potential. The P50 potential is a midlatency auditory evoked potential that is (a) rapidly habituating, (b) sleep state-dependent, and (c) generated in part by cholinergic elements of the Reticular Activating System (the RAS modulates sleep-wake states, arousal, and fight versus flight responses). Using a paired stimulus paradigm, sensory gating of the P50 potential has been found to be reduced in such disorders as anxiety disorder (especially post-traumatic stress disorder, PTSD), depression, and schizophrenia (Garcia-Rill 1997). Another "preattentional" measure, the startle response, could be used; however due to its marked habituation — measurement time is too prolonged (>20 min) — and because compliance using startling, loud stimuli could also be a problem, the use of the P50 potential is preferable.

Sensory gating deficits can be induced by stress and thus represent a serious impediment to proper performance under complex operational demands. *We propose the development of a nanoscale module designed for the use of the P50 potential as a measure of sensory gating (Figure C.9).*

A method to assess performance readiness could be used as a predictor of performance success, especially if it were noninvasive, reliable, and not time-consuming. If stress or other factors have produced decreased sensory gating, then remedial actions could be instituted to restore sensory gating to acceptable levels, e.g., coping strategies, relaxation techniques, pharmacotherapy. It should be noted that this technique also may be useful in detecting slowly developing (as a result of cumulative stress) chronic sensory gating deficits that could arise from clinical depression or anxiety disorder, in which case remedial actions may require psychopharmacological intervention with, for example, anxiolytics or antidepressants.

Implementation of this methodology would be limited to the ability to record midlatency auditory evoked responses in varied environments. The foreseen method of implementation would involve the use of an electronically shielded helmet (Figure C.9) containing the following: (1) P50 potential recording electrodes at the vertex, mastoids, and ground; (2) eye movement recording using a flip-down transparent screen to monitor the movements of one eye within acceptable limits that do not interfere with P50 potential acquisition; and (3) electrodes on the forehead to monitor muscle contractions that could interfere with P50 potential acquisition. The helmet would incorporate an audio stimulator for delivering click stimuli, operational amplifiers for the three measures, averaging software, wave detection software (not currently available), and simple computation and display on the flip-down screen of sensory gating as a percent. A high percentage compared to

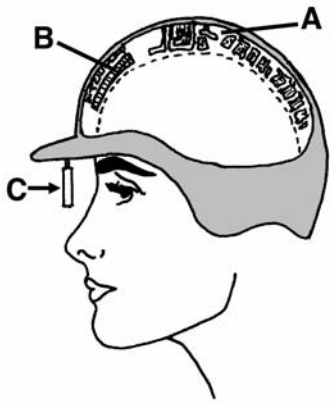

Figure C.9. Nanotechnology application: helmet incorporating P50 midlatency auditory evoked potential recording and near-infrared detection of frontal lobe blood flow to measure sensory gating and hypofrontality, respectively. A. Evoked potential module including audio stimulator (earphones), surface electrodes (vertex, mastoids, forehead), amplifiers, averager with wave recognition software, and data storage device for downloading. B. Near-infrared detection module for frontal lobe blood flow measurement. C. Flip-down screen for tracking eye movements and display of results from sensory gating and frontal blood flow measurements.

control conditions would be indicative of a lack of sensory gating (indicating increased distractibility, uncontrolled anxiety, etc.). An individual could don the helmet and obtain a measure of sensory gating *within 5-7 minutes.*

The applications for this nanotechnology would be considerable, including military uses for self-monitoring human performance in advance of and during critical maneuvers; for self-monitoring by astronauts on long-duration space missions; for pilots, drivers, and operators of sensitive and complex equipment, etc. It should be noted that this physiological measure can not be "faked" and is applicable across languages and cultures.

Hypofrontality

In general, the role of the frontal cortex is to control, through inhibition, those old parts of the brain we inherited from our early ancestors, the emotional brainstem (Damasio 1999). If the frontal cortex loses some of its inhibitory power, "primordial" behaviors are released. This can occur when the cortex suffers from decreased blood flow, known as "hypofrontality." Instinctive behaviors then can be released, including, in the extreme, exaggerated fight versus flight responses to misperceived threats, i.e., violent behavior in an attempt to attack or flee. "Hypofrontality" is evident in such disorders as schizophrenia, PTSD, and depression, as well as in neurodegenerative disorders like Alzheimer's and Huntington's diseases. Decreased frontal lobe blood flow can be induced by alcohol. Damage, decreased uptake of glucose, reduced blood flow, and reduced function have all been observed in the frontal cortex of violent individuals and murderers.

The proposed method described below could be used to detect preclinical dysfunction (i.e., could be used to *screen and select* crews for military or space travel operations); to determine individual performance under stress (i.e., could be used to *prospectively evaluate* individual performance in flight simulation/virtual emergency conditions); and to monitor the effects of chronic stressors (i.e., monitor sensory gating during long-duration missions). This nanomethodology would be virtually realtime; would not require invasive measures (such as sampling blood levels of cortisol, which are difficult to carry out accurately and are variable and delayed rather than predictive); and would be more reliable than, for example, urine cortisol levels (which would be delayed or could be compensated for during chronic stress). Training in individual and communal coping strategies is crucial for alleviating some of the sequelae of chronic stress, and the degree of effectiveness of these strategies could be *quantitatively assessed* using sensory gating of the P50 potential as well as frontal lobe blood flow. That is, these measures could be used to determine the efficacy of any therapeutic strategy, i.e., to measure outcome.

A detecting module located over frontal areas with a display on the flip-down screen could be incorporated in the helmet to provide a noninvasive measure of frontal lobe blood flow for self-monitoring in advance of critical maneuvers. The potential nanotechnology involved in such measures has already been addressed (Chance and Kang n.d.). Briefly, since hemoglobin is a strong absorber, changes in this molecule could be monitored using near-infrared detection. This promising field has the potential for monitoring changes in blood flow as well as hemoglobin saturation, a measure of energy usage.

Peripheral nanotechnology applications such as P50 potential recordings and frontal blood flow measures are likely to provide proximal, efficient, and useful

improvements in human performance. Nanotechnology, by being transparently integrated into our executive functions, will become part of the enculturation process, modulating brain structure and driving our evolution.

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SCIENCE AND TECHNOLOGY AND THE TRIPLE D (DISEASE, DISABILITY, DEFECT)

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Science and technology (S&T) have had throughout history — and will have in the future — positive and negative consequences for humankind. S&T is not developed and used in a value neutral environment. S&T activity is the result of human activity imbued with intention and purpose and embodying the perspectives, purposes, prejudice and particular objectives of any given society in which the research takes place. S&T is developed within the cultural, economical, ethical, and moral framework of the society in which the research takes place. Furthermore, the results of S&T are used in many different societies reflecting many different cultural, economical, ethical, moral frameworks. I will focus on the field of Bio/Gene/Nanomedicine. The development of Bio/Gene/Nanotechnology is — among other things — justified with the argument that it holds the promises to fix or help to fix perceived disabilities, impairments, diseases, and defects and to diminish suffering. But who decides what is a disability, disease, an impairment and a 'defect' in need of fixing? Who decides what the mode of fixing (medical or societal) should be, and who decides what is suffering? How will these developments affect societal structures?

Perception

The right answers to these questions will help ensure that these technologies will enhance human life creatively, rather than locking us into the prejudices and misconceptions of the past. Consider the following examples of blatant insensitivity:

> Fortunately the Air Dri-Goat features a patented goat-like outer sole for increased traction so you can taunt mortal injury without actually experiencing it. Right about now you're probably asking yourself

> "How can a trail running shoe with an outer sole designed like a goat's hoof help me avoid compressing my spinal cord into a Slinky on the side of some unsuspecting conifer, thereby rendering me a drooling, misshapen non-extreme-trail-running husk of my former self, forced to roam the earth in a motorized wheelchair with my name embossed on one of those cute little license plates you get at carnivals or state fairs, fastened to the back?" (Nike advertisement, Backpacker Magazine, October 2000).
>
> Is it more likely for such children to fall behind in society or will they through such afflictions develop the strengths of character and fortitude that lead to the head of their packs? Here I'm afraid that the word handicap cannot escape its true definition — being placed at a disadvantage. From this perspective seeing the bright side of being handicapped is like praising the virtues of extreme poverty. To be sure, there are many individuals who rise out of its inherently degrading states. But we perhaps most realistically should see it as the major origin of asocial behavior (Watson 1996).

American bioethicist Arthur Caplan said in regards to human genetic technology, "the understanding that our society or others have of the concept of health, disease, and normality will play a key role in shaping the application of emerging knowledge about human genetics" (Caplan 1992). I would add Nanomedicine/Nanotechnology into Caplan's quote because parts of nanotechnology development are inherently linked with bio/genetechnology as the following quote from a recent report on its societal implications illustrates:

> Recent insights into the uses of nanofabricated devices and systems suggest that today's laborious process of genome sequencing and detecting the genes' expression can be made dramatically more efficient through use of nanofabricated surfaces and devices. Expanding our ability to characterize an individual's genetic makeup will revolutionize diagnostics and therapeutics (Roco and Bainbridge 2001).

In addition, nanomedicine and nanotechnologies must be added, to quote the report again, because they

> ...hold promise for contributing to a wide range of assistive solutions, from prosthetic limbs that adjust to the changes in the body, to more biocompatible implants, to artificial retinas or ears. Other opportunities lie in the area of neural prosthesis and the "spinal patch," a device envisioned to repair damage from spinal injuries (Roco and Bainbridge 2001).

Any of these solutions are linked to the normalcy concept, the ability concept, and to the perceptions of what needs to be assisted. Certainly, different responses will be made and different solutions will be sought depending on how the problem is defined; and how the problem will be defined depends on our concepts of and beliefs about such things as health, disease, disability, impairment, and defect. For example, whether being gay is seen as a disease and defect (medical model) or a variation of human diversity (social model) will lead to totally different intervention

scenarios (medical cure versus social cure). In the same way, what if we would view women as a double X syndrome, or men as an XY syndrome?

In essence every biological reality can be shaped and seen as a defect, as a medical problem, or as a human rights and social problem. No one views nowadays — in western culture at least — the biological reality of being a women within a medical framework, although a women was still viewed at the end of last century in countries like the United Kingdom as too biologically fragile and emotional and thus too dependent, to bear the responsibility attached to voting, owning property, and retaining custody of their own children (Silvers et. al., 1998). Therefore, a societal cure of equal rights and respect is seen as the appropriate remedy for the existing disparity between women and men. Gays, lesbians, bisexuals, and other groups demand that their problems be seen within a social framework and not within a medical framework.

So what now about so-called disabled people? Are "disabled people" or differently said "people who do not fit society's expectation of normal ability" to be seen as a medical problem or as part of the diversity of humankind? Within the medical model, disability is viewed as a defect, a problem inherent in the person, directly caused by disease, trauma, or other health condition and a deviation from certain norms. Management of the disability of the disabled person or person-to-be is aimed at cure, prevention, or adaptation of the person (e.g. using assistive devices). Medical care and rehabilitation are viewed as the primary issues, and at the political level, the principal response is that of modifying or reforming health care policy.

The social model of disability, on the other hand, sees the issue mainly as a socially created problem and principally as a matter of the full integration of individuals into society. Disability is not an attribute of an individual, but rather a complex collection of conditions, many of which are created by the environment, particularly the social environment and socially mediated aspects of the physical environment. Hence, the management of the problem requires social action, and it is the collective responsibility of society at large to make the environmental modifications necessary for the full participation of people with disabilities in all areas of social life. The issue is therefore an attitudinal or ideological one requiring social change, which at the political level becomes a question of human rights to be seen in the same way as the issues of gender and sexual orientation. In essence able-ism is seen in the same light as racism, sexism, age-ism, homophobia, etc.

The social model of disability does not negate that a disabled person has a certain biological reality (like having no legs), which makes her/him different in her/his abilities, which make her/him not fit the norm. But it views the "need to fit a norm" as the disability and questions whether many deviations from the norm need a medical solution (adherence to the norm) or a social solution (change/elimination of norm).

Many bio/gene/nano technology applications (predictive testing, cures, adaptation) focus on the individual and his or her perceived shortcomings. They follow a medical, not a social evaluation of a characteristic (biological reality) and therefore offer only medical solutions (prevention or cure/adaptation) and no social solutions (acceptance, societal cures of equal rights and respect).

Furthermore the use and development focus of bio/gene/nanotechnology as it is perpetuates the medical, intrinsic, individualistic, defect view of disability. Not often discussed by clinicians, academics in general, or the general public is the view, commonly expressed by disabled people, that the demand for the technology is based too much on the medical model of disability and hardly acknowledges the social model of disability (Asch 1999, Miringoff 1991; Hubbard 1990: Lippman 1991; Field 1993; Fine & Asch 1982; Minden 1984; Finger 1987; Kaplan 1994; Asch 1989; Asch and Geller 1996).

The perception of disabled people as suffering entities with a poor quality of life, in need of cure and fixing, for the most part does not fit with the perceptions disabled people have of themselves. This fact is illustrated by Table C.5, which compares self esteem of people having spinal cord injury with the images many nondisabled people have of what this hypothetically would mean for themselves.

Table C.5: Self-esteem ratings following severe spinal cord injury (SCI)

Percent agreeing with each statement	Nondisabled Respondents	Nondisabled Respondents Imagining Self with SCI	SCI Survivors Comparison Group
I feel that I am a person of worth.	98%	55%	95%
I feel that I have a number of good qualities.	98%	81%	98%
I take a positive attitude.	96%	57%	91%
I am satisfied with myself on the whole.	95%	39%	72%
I am inclined to feel that I am a failure.	5%	27%	9%
I feel that I do not have much to be proud of.	6%	33%	12%
I feel useless at times.	50%	91%	73%
At times I feel I am no good at all.	26%	83%	39%

Clearly, most people with spinal cord injury have positive self-images, but nondisabled people have the false impression that a person with this injury would lack self-esteem. This table was adapted from Gerhart et al., 1994, but many other studies report similar findings (Cameron 1973; Woodrich and Patterson 1983; Ray and West 1984; Stensman 1985; Bach and Tilton 1994; Cushman and Dijkers 1990; Whiteneck et al. 1985; Eisenberg and Saltz 1991; Saigal et al. 1996 Tyson and Broyles 1996; Cooley et al. 1990).

The following passage provides an example of how many professionals view the effects of people with disabilities on their families.

> How did parents endure the shock [the birth of a thalidomide baby]? The few who made it through without enormous collateral damage to their lives had to summon up the same enormous reserves of courage and devotion that are necessary to all parents of children with special needs and disabilities; then, perhaps, they needed still more courage, because of the special, peculiar horror that the sight of their children

> produced in even the most compassionate. Society does not reward such courage… because [what] those parents experience represents our own worst nightmare, ever since we first imagined becoming parents ourselves. The impact upon the brothers and sisters of the newborn was no less horrific. This was the defining ordeal of their family life — leaving aside for now the crushing burden on their financial resources from now on (Stephens and Brynner 2001).

While such negative views of the impact of children with disabilities on their families have dominated clinical and research literature for decades, more recent research has exposed these negative biases as empirically unsupportable and clinically destructive (e.g., Helf and Glidden, 1998; Sobsey, 1990). Contemporary research suggests that parents, like people with disabilities, do not view their children with disabilities as their "worst nightmares," as sources of "peculiar horror" or as "crushing burdens." In fact, most view them very much as they view children without disabilities, as sources of significant demands but even greater rewards (e.g., Sobsey & Scorgie 2001). Yet, people with disabilities and their families are a part of society and they can never be entirely free of the attitudes, beliefs, and biases held by professionals and the general public.

Such attitudes and beliefs about disability contribute to the drive to fix people with disabilities rather than accommodate them. For example, the quote from Stephens and Brynner seems to suggest:

1. an implicit assumption of normalcy which requires two legs and two arms
2. an expectation that everyone has to be able to perform certain functions (e.g., move from one place to another or eat)
3. an expectation that everyone has to perform this function in a the same way (e.g., walking upright on their own legs or eat with their hands)
4. an expectation that any variation in form, function, method will result in severe emotional distress for those involved in any way

These attitudes drive the development of artificial legs and arms and help to explain why thalidomide kids and their parents were confronted with the single-minded approach to outfit thalidomide kids with artificial limbs without exploring different forms of functioning. Professionals typically persisted with this approach in spite of the fact that artificial limbs were rather crude, not very functional, and mostly cosmetic at the time and that they were being prescribed in great numbers. The approach nearly completely excluded alternatives, such as crawling in the absence of legs or eating with one's feet in the absence of arms. The sentiment expressed by Stephens and Brynner also prevents adaptation by society to alternative modes of function (e.g., moving and eating).

This kind of single-minded approach reflects an adherence to a certain norm, which was more readily accepted by amputees who lost their arms or legs. They were or are willing to accept this because in a large part due to the fact that they were not allowed to adapt and get used to their new condition, a process that we all know takes time. People take time to adapt to any change. Humankind is not known for its ability to adapt easily to changes (e.g., divorce, career changes). Thalidomiders did not have to readapt to a new body reality. That might explain why most Thalidomiders threw away their artificial legs and arms as soon as they

were old enough to assert themselves against their parents and the medical profession. For them the reality was that they did not view their body as deficient and did not see artificial legs or arms as the most suitable mode of action. In light of the perception reflected in the Stephens and Brynner's quote, the question becomes whether the development of usable artificial legs and arms mean that someone without legs or arms will be even more stigmatized if he or she does not use them. If so, the presence of this option is not merely another free choice since existence of the option results in a coercive influence on those who might refuse it.

Choice

The question arises whether usable artificial limbs increase choice as an optional tool or establish a norm that restricts choice. Parents of Thalidomiders were not given much choice. Immense pressure was used to have the parents equip their kids with artificial limbs. Society already judges certain tools. A hierarchy regarding movement exists. Crawling is on the bottom of the acceptance list, below the wheelchair, which is seen as inferior to the artificial leg, particularly one that appears "natural." This hierarchy is not based on functionality for the person but rather on emotions, prejudice, and rigid adherence to a normative body movement. Tools like the wheelchair are frequently demonized in expressions such as "confined to the wheelchair." It is interesting that people do not say "confined to" artificial legs even though a wheelchair often leads to safer, easier, and more efficient mobility for an individual than artificial legs do. No one would use the phrase "confined to natural legs" for "normal" people, although in reality they are confined to their legs while many wheelchair users can leave their wheelchairs. Similarly, the negative concept of confinement is not used to describe driving a car, which is viewed as empowering rather than limiting, even though many of us are heavily dependent on this mode of transportation. In much the same way, most of us who live in the north would not survive a single winter without central heating, but we generally do not label ourselves as "technology dependent."

Cochlear implants provide another related example. Do we allow parents to say "No" to them if they feel there is nothing wrong with their kid using sign language, lip reading, or other modes of hearing? Will the refusal by the parents be viewed as child abuse (see Harris, 2000 for an ethical argument to view it as child abuse)? Might parents have been considered to commit child abuse if they had refused artificial limbs for their Thalidomide kids? Or in today's world, could a mother be considered to commit child abuse if she refused to terminate her pregnancy after ultrasound showed phocomelia (i.e., hands and feet attached close to the body without arms or legs) in the fetus. Of course, ultrasound wasn't an option when most of the Thalidomide cases occurred, but it is today. Furthermore, would the mother abuse society by not fixing (cure, adaptation, prevention) the "problem"?

A hint to the answer to these questions is given by the following results of a survey of genetic counselors in different countries (Wertz 1998):

> The majority in 24 countries believed it is unfair to the child to be born with a disability. 40% agreed in the USA, Canada, and Chile. 36% in Finland and the UK; 33% in Switzerland and the Netherlands; 29% in Argentina, 27% in Australia, 25% in Sweden, and 18% in Japan.

> It is socially irresponsible knowingly to bring an infant with a serious [no legal document defines what is serious] genetic disorder into the world in an era of prenatal diagnosis." More than 50% agreed in South Africa, Belgium, Greece, Portugal, the Czech Republic, Hungary, Poland, Russia, Israel, Turkey, China, India, Thailand, Brazil, Columbia, Cuba, Mexico, Peru, and Venezuela. 26% of U.S. geneticists, 55% of U.S. primary care physicians, and 44% of U.S. patients agreed.
>
> A high percentage of genetic counselors feels that societies will never provide enough support for people with disabilities. The percentage of agreement for the statement ranges from 18% as a lowest to 80% in the U.K. Germany is in the middle with 57%. The U.S.A. has a number of 65%.

These statements suggest that women don't have a free choice but are led to follow the path of medical intervention. In the absence of a possible social cure for disability, the only option left that may appear to be available is the medical cure in whatever shape and form, independent of its usefulness and need.

The treatment of Thalidomiders, the pressure to install cochlear implants, and prebirth counseling raise a more general question about whether advances in a wide range of assistive devices, partly due to advances in micro- and nanotechnologies, will lead to increased or restricted choices. We can hope that technological convergence offers humanity so many choices that false stereotypes about the disabled are discredited once and for all. But this can happen only if we recognize the alternatives as real choices that must be considered with sensitivity, imagination, and — most importantly — the judgment of disabled people themselves.

Consequences

The history of the debate around bio/gene/nano-technology as it relates to disability shows a strong bias towards a medical, individualistic, intrinsic defect view of disability focusing on medical/technological cures without addressing societal components. People who promote the use of bio/genetechnology often denounce the social model of disability (Harris 2000; Singer 2001).

The medical model of disability can also show itself in court rulings, such as some recent U.S. Supreme Court rulings. The Supreme Court ruled on the "definition of disability" in Sutton v. United Airlines (130 F.3d 893, 119 S. Ct. 2139), Albertsons Inc. v. Kirkingburg (143 F.3d 1228, 119 S. Ct. 2162), and Murphy v. United Parcel (141 F.3d 1185, 119 S. Ct. 1331), stating that the Americans with Disabilities Act does not cover those persons with correctable impairments.[2] In other words, as soon as adaptations are available, all problems must be fixed and no protections through civil rights laws, such as the ADA, are allowed anymore. Not only that, the ruling implies that disability is something that can be fixed through medical technological means. A social view of disability does not fit with the above ruling.

[2] National Council on Disability USA, 2000; Civil Rights, Sutton v. United Airlines, Albertsons Inc. v. Kirkingburg, and Murphy v. United Parcel (http://www.ncd.gov/newsroom/publications/policy98-99.html#1).

We see a disenfranchisement of disabled people from the equality/human rights movement. (Wolbring 1999, 2000, and 2001). So far, bio/genetechnology has led to an increase in discrimination against characteristics labeled as disabilities, as the following three examples illustrate.

First, we see a proliferation of legal cases involving wrongful life or wrongful birth suits (Wolbring, 2001,2002a). Wrongful life suits are only accepted if the child is disabled. And wrongful birth suits are specific by now for disability with special rulings whereas cases based on non-disability are called wrongful pregnancy. The remedies in the case of wrongful birth/pregnancy cases are quite different. The following quotations illustrate the logic of such cases.

> Two other justices based their agreement of wrongful life suits on the view that the physician's wrongful life liability towards the disabled infant rests on the right to life without a handicap. Thus the damage is measured by comparing the actual impaired life of the plaintiff to a hypothetical unimpaired life (CA 518, 540, 82 Zeitzoff versus Katz (1986) 40 (2) PD 85 Supreme Court of Israel (482); Shapiro 1998).

> ...in essence … that [defendants] through their negligence, [have] forced upon [the child] the worse of … two alternatives, … that nonexistence — never being born — would have been preferable to existence in the diseased state (Soeck v. Finegold, 408 A.2d 496(Pa. 1970)).

> "Thus the legislature has recognized," the judge said, "as do most reasonable people, that cases exist where it is in the interest of the parents, family, and possibly society that it is better not to allow a fetus to develop into a seriously defective person causing serious financial and emotional problems to those who are responsible for such person's maintenance and well-being (Strauss 1996).

Second, anti-genetic discrimination laws cover discrimination on genetic characteristics which might lead in the future to 'disabilities' in a medical sense but are for the time being asymptomatic. In essence, the feature of genetic discrimination is the use of genetic information about an asymptomatic disabled person. The vogue for the establishment of an Anti-Genetic Discrimination law for asymptomatic disabled people highlights one other reality, namely that symptomatic disabled people are excluded from exactly the benefits the Anti-Genetic Discrimination laws try to address. With the new laws these symptomatic disabled people will still be discriminated against whereas the asymptomatic ones will be safe. Not only that, ability becomes a measure to justify these new laws, as the following statement from the American Civil Liberties Union illustrates.

> The ACLU believes that Congress should take immediate steps to protect genetic privacy for three reasons. First, it is inherently unfair to discriminate against someone based on immutable characteristics that do not limit their abilities... (ACLU 2000)

> In sum, the ACLU believes that Americans should be judged on their actual abilities, not their potential disabilities. No American should lose a job or an insurance policy based on his or her genetic predisposition. (ACLU 2000)

A third consequence of the current mindset is differential use of predictive genetic testing. We see an Animal Farm Philosophy in regards to what to test for. Testing to eliminate any so-called disability, disease, defect is acceptable; but testing to determine and select on the basis of a characteristic like sex is not (Wolbring 2000, 2001).

Where should we go from here? To prevent further stigmatization, recommendations such as those quoted below from the UNESCO World Conference on Sciences 1999 conference should be implemented.

> 25. ...that there are barriers which have precluded the full participation of other groups, of both sexes, including disabled people, indigenous peoples and ethnic minorities, hereafter referred to as "disadvantaged groups..."
>
> 42. Equality in access to science is not only a social and ethical requirement for human development, but also a necessity for realizing the full potential of scientific communities worldwide and for orienting scientific progress towards meeting the needs of humankind. The difficulties encountered by women, constituting over half of the population in the world, in entering, pursuing, and advancing in a career in the sciences and in participating in decision-making in science and technology should be addressed urgently. There is an equally urgent need to address the difficulties faced by disadvantaged groups, which preclude their full and effective participation.

Thus, it is essential that the greatest possible diversity of people participate in the development of convergent technologies and contribute to the associated sciences:

> 17. Scientists, research institutions, and learned scientific societies and other relevant non-governmental organizations should commit themselves to increased international collaboration including exchange of knowledge and expertise. Initiatives to facilitate access to scientific information sources by scientists and institutions in the developing countries should be especially encouraged and supported. Initiatives to fully incorporate women scientists and other disadvantaged groups from the South and North into scientific networks should be implemented. In this context efforts should be made to ensure that results of publicly funded research will be made accessible.
>
> 79. The full participation of disadvantaged groups in all aspects of research activities, including the development of policy, also needs to be ensured.
>
> 81. Governments and educational institutions should identify and eliminate, from the early learning stages, educational practices that have a discriminatory effect, so as to increase the successful participation in science of individuals from all sectors of society, including disadvantaged groups.

> 91. Special efforts also need to be made to ensure the full participation of disadvantaged groups in science and technology, such efforts to include:
>
> removing barriers in the education system;
>
> removing barriers in the research system;
>
> raising awareness of the contribution of these groups to
>
> science and technology in order to
>
> overcome existing stereotypes;
>
> undertaking research, supported by the collection of data,
>
> documenting constraints;
>
> monitoring implementation and documenting best practices;
>
> ensuring representation in policy-making bodies and forums (UNESCO 2000)

We should strive to eliminate able-ism and promote the acceptance of diversity in abilities for the sake of humankind as the best defense against gene-ism, which might affect 60 percent of society according to a New Zealand study. This acceptance of diverse abilities is actually also needed for the thriving of assistive technologies. For example, if an assistive technology leads to better vision than humankind has normally, should we discard the now majority of people who are less able? Or should we force all to use the new adaptive devices? Or should we demonize the ones who are more able?

The labeling of people and groups within a medical disease defect model against their will is unacceptable. In essence every scientist whose work has societal consequences has to become a societal activist to prevent these consequences.

Conclusion

The views expressed here are not opposed to progress in science and technology. As a lab bench biochemist, it would be strange for me to oppose S&T in general. Rather, this essay emphasizes the importance of openness to different perspectives on what qualifies as progress (Wolbring, 2002b). Science and technology can be extremely useful, but certain perceptions, stereotypes, and societal dynamics can lead scientists and engineers to focus on certain types of S&T, quite apart from their objective utility to potential users.

This is not merely an issue of fairness to diverse groups of people, including the disabled. It is also an issue of imagination and insight. Convergent technologies will accomplish much more for humanity, and unification of science will lead to much greater knowledge, if they are free of the ignorant prejudices of the past. Specifically, science and engineering will benefit from the varied perspectives that the disabled may have about what it means to improve human performance. One essential tool to achieve this is to make sure that the teams of researchers, designers, and policy makers include many talented people who happen to be disabled.

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VISIONARY PROJECTS

BRAIN-MACHINE INTERFACE VIA A NEUROVASCULAR APPROACH

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The issue of brain-machine (computer) interface is, without doubt, one of the central problems to be addressed in the next two decades when considering the role of neuroscience in modern society. Indeed, our ability to design and build new information analysis and storage systems that are sufficiently light to be easily carried by a human, will serve as a strong impetus to develop such peripherals. Ultimately, the brain-machine interface will then become the major bottleneck and stumbling block to robust and rapid communication with those devices.

So far, the interface improvements have not been as impressive as the progress in miniaturization or computational power expansion. Indeed, the limiting factor with most modern devices relates to the human interface. Buttons must be large enough to manipulate, screens wide enough to allow symbol recognition, and so on. Clearly, the only way to proceed is to establish a more direct relation between the brain and such devices, and so, the problem of the future brain-machine interface will indeed become one of the central issues of modern society. As this is being considered, another quite different revolution is being enacted by the very rapid and exciting developments of nanotechnology (n-technology). Such development deals with manufactured objects with characteristic dimensions of less than one micrometer. This issue is brought to bear here, because it is through n-technology that the brain-machine bottleneck may ultimately be resolved. Obviously, what is required is a robust and noninvasive way to both tap and address brain activity optimized for future brain-machine interaction.

Needless to say, in addition to serving as a brain-machine interface, such an approach would be extraordinarily valuable in the diagnosis and treatment of many neurological and psychiatric conditions. Here, the technology to be described will be vital in the diagnosis and treatment of abnormal brain function. Such technology would allow constant monitoring and functional imaging, as well as direct modulation of brain activity. For instance, an advanced variation of present-day deep brain stimulation will be of excellent therapeutic value. Besides, interface with "intelligent" devices would significantly improve the quality of life of disabled individuals, allowing them to be more involved in everyday activity.

The problem we consider has two main parts to be resolved: (1) hardware and (2) software. To approach these issues, we propose to develop a new technology that would allow *direct* interaction of a machine with the human brain and that would be secure and minimally invasive.

The Neurovascular Approach

One of the most attractive possibilities that come to mind in trying to solve the hardware problem concerns the development of a vascular approach. The fact that the nervous system parenchyma is totally permeated by a very rich vascular bed that supplies blood gas exchange and nurturing to the brain mass makes this space a very

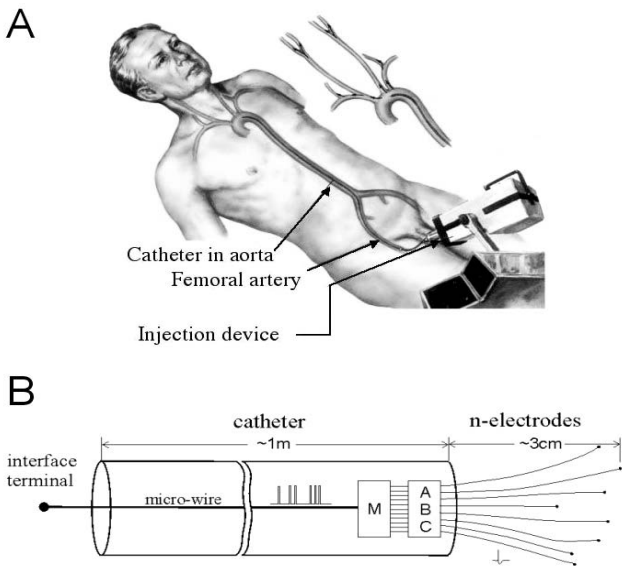

Figure C.10. The neurovascular approach. A. Present day procedure utilized to guide catheters to the brain via the vascular system. Catheters are introduced into femoral, subclavial, or carotid artery. B. The general electronic design includes n-electrodes (diameter of 0.5 micron and length not more than 3 cm) to record/stimulate neuronal activity; Amplifier-Binary Converter (ABC) block that converts acquired analog signals into binary form; Multiplex (M) unit that transforms analog input into serial form by fast switching between all signals; and microwire (approx. 1 m long) that conveys information to the terminal. (Only one logic set is shown.)

attractive candidate for our interface. The capillary bed consists of 25,000 meters of arterio-venous capillary connections with a gauge of approximately 10 microns. At distances more proximal to the heart, the vessels increase rapidly in diameter, with a final dimension of over 20 millimeters. Concerning the acquisition of brain activity through the vascular system, the use of n-wire technology coupled with n-technology electronics seems very attractive. It would allow the nervous system to be addressed by an extraordinarily large number of isolated n-probes via the vascular bed, utilizing the catheter-type technology used extensively in medicine and in particular in interventional neuro-radiology.

The basic idea consists of a set of n-wires tethered to electronics in the main catheter such that they will spread out in a “bouquet” arrangement into a particular portion of the brain’s vascular system. Such arrangement could support a very large number of probes (in the millions). Each n-wire would be used to record, very securely, electrical activity of a single or small group of neurons without invading the brain parenchyma. Obviously, the advantage of such system is that it would not interfere with either the blood flow exchange of gases or produce any type of disruption of brain activity, due to the tiny space occupied in the vascular bed.

In order to give a more precise description of the proposed interface, an illustration of the procedure is shown in Figure C.10. A catheter is introduced into

the femoral carotid or the sub-clavial artery and is pushed up to one of the vascular territories to be addressed. Such procedure is, in principle, similar to interventional neuro-radiology techniques where catheters are guided to any portion of the central nervous system. The number of 0.5 micron diameter wires (recording points) that could be introduced in a one-millimeter catheter is staggeringly large (in the range of few million). Once the areas to be recorded or stimulated are reached, a set of leads held inside the catheter head would be allowed to be extended and randomly distributed into the brain's circulatory system. Since a catheter can be placed in any major brain vessels, the maximum length of n-wire electrodes required to reach any capillary bed is of the order 2 to 3 cm. Hence, a large number of electrodes would cover any region of the central nervous system from the parent vessels harboring the stem catheters.

General Electronic Design

A number of single n-wire electrodes can be attached via amplifier-binary converter to a multiplex amplifier that would sequentially switch between large, "simultaneously recorded" electrical brain signals (Figure C.10B). This is possible since the switching properties of modern multiple amplifiers are many orders of magnitude faster than the electrical signals of the brain. Thus, the number of independent wires necessary to convey the information down to the terminals of the interface would be a small fraction of the total number of n-wires, and thus, inexpensive and robust microwires can be used along the catheter length.

Many technical issues concerning hardware problems, such as n-amplifiers and multiplex units, can in fact be solved by present technology. The actual size of the expected extracellular recording wiring is given inFigure C.11 by comparing the size of one-micrometer wire with the size of a capillary in the brain parenchyma. In this case, an individual Purkinje cell is drawn to show where the capillary spaces reside within the dendritic tree of such neurons. Note that the number of capillaries

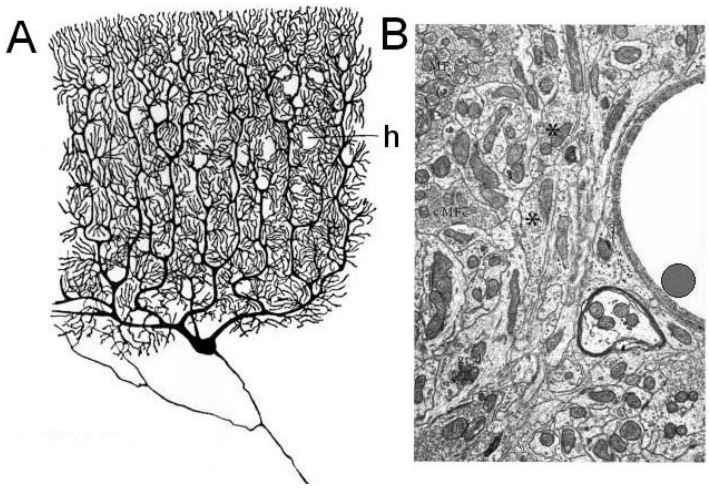

Figure C.11. Illustration of comparative size scales for a neuron, a capillary, and an n-wire. A. Purkinje cell with dendritic tree penetrated by many capillaries foramen. h. B. Elentronmicrograph of a corresponding site in the dendritic as shown in h with a 1µ electrode (spot) drawn inside a capillary.

traversing each cell is numerous (in this particular case, more than 20). On the right inset is an electron micrograph of the same area that gives an accurate representation of the size relation between one such n-wire (in this case 0.9 micron) and the diameter of the smallest of capillaries in that portion of brain parenchyma.

Thus, at this point, the materials and methodology required to implement a mega electrode system are basically within our technology over the next decade.

Software Requirements

The second significant issue is that of the computational requirements that would allow the reading, storing, and contextualizing of the enormous amount of neuronal information that would become available with the vascular approach described above. While this may prove to be more challenging than the hardware component of this interface, it would also be most valuable, as the proper understanding of such activity would give us an significant window into brain function, further defining the relations between electrophysiology and cognitive/motor properties of the brain.

Attempting to investigate this problem, the second step in this proposal, would be the development of mathematical algorithms able to classify brain states based on neuronal unit activity and field potential analysis. Initially, we plan to correlate, in real time, the moment-to-moment electrical activity of neurons with large functional brain states. It is assumed that the electrical properties of neurons define all possible brain states and that such states co-vary systematically with the global state dynamics. However, this does not imply that there exists one-to-one correspondence between purely local patterns of brain activity and a particular set of functional states. The generation of a new functional state in the brain, for instance, transition "sleep-wakefulness," is known to correspond to activity reorganization over many groups of neurons. Needless to say, there is a large number of possible patterns that differs minimally from one other. The approach is to map the small variance patterns into relatively small sets of different functional states. For example, in the simplest case only three global functional states may be considered: (1) sleep, (2) wakefulness, and (3) "none of the above" or uncertain state, e.g., drowsiness. The last state is an absolutely necessary form to be included, for two reasons: (a) mathematically, the output domain of the algorithm must be closed in order to address correctly "any possible input pattern," including those that have unavoidable noise impact or belong to intermediate, non-pure states without a reliable answer within statistical significance level; and (b) from the conceptual viewpoint, the third state is vital, as for instance, seeing can only occur during wakefulness, and during sleep, this state is uncertain.

The design of the hardware part of the interface (see Figure C.10B) has not been dictated by electronic purposes only but also pursues the goal of preliminary signal processing. Here, we use the commonly accepted hypothesis that neurons interact with each other mostly via action potentials and related synaptic interactions. Thus, it seems to be natural to convert electrical signals taken from n-electrodes into binary form. This approach has many advantages. In particular, if the threshold level for digitalization is appropriately chosen, we would be able to overcome the following problems:

- Not all electrodes would be placed at "right" positions (some of them may be far enough from any neuron to produce reliable data), or just damaged.

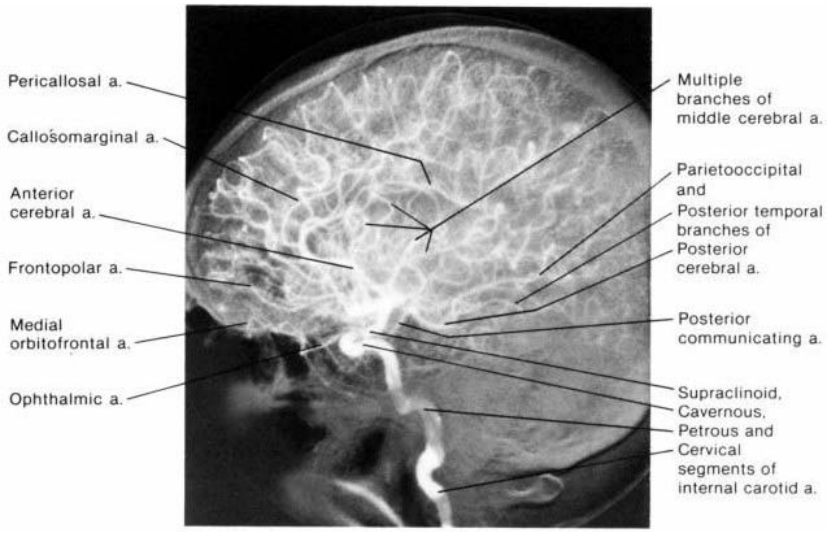

Figure C.12. Lateral view of brain arteries.

- Two electrodes placed in vicinity of a single neuron but at diverse distances from it will produce output voltage traces of different amplitude.
- The signal-to-noise ratio may not be optimal if an electrode records from more than one neuron, as one of them may be selected and others suppressed by the threshold system.

Moreover, binary form is computer friendly and supports efficient operation. Also additional processing logic can be easily included between a computer and the terminals of microwires that would significantly speed up data acquisition, storage, and contextualization.

Memory Requirements

A rough estimate of memory requirements to support resident information and input bandwidth (informational flow rate) will be $10^6 \times 10^3 = 10^9$ bits/s, assuming input signals from 10^6 independent binary variables with a sampling rate of 1 kHz. That is 100 MB per second for the total output, which is attainable with present day technologies. Utilization of additional intermediate logic would even afford a greater performance increase.

Classification Algorithms

As mentioned above, the computational algorithm must be designed to spot alterations in the brain activity that relate to a global change of states. This activity is represented by the set of binary time series taken from many neurons, i.e., by spatiotemporal patterns. Thus, we have the pattern classification problem mentioned above. For an algorithm to be useful, it must be optimized to (1) determine the minimal number of hypotheses (possible functional states) concerning the data set; (2) economize on data storage and subsequent data manipulation/calculation; (3)

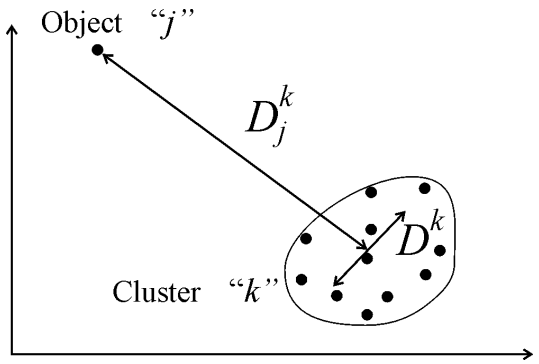

Figure C.13. Qualitative illustration of dissimilarity of object "j" to cluster "k" and mean dissimilarity within the cluster.

scale for increasing data sets and for the number of functional states; and (4) be robust. The approach to the problem we propose below is based on *cluster analysis* (Kaufman 1990) and measures of dissimilarity between time series (see, for example, Kantz 1994; Schreiber 1997; Schreiber and Schmitz 1997).

In the first step, the data set will be split into *J* short time intervals by shifting a time window of length *T*. The time scale *T* can be varied for different purposes, and its choice is a compromise between speed and reliability in data analysis. Each window will be referred to as "an object" or entity, assuming that a window encompasses an unchanged functional state. Assuming a correct set of hypotheses concerning the number of clusters, *K*, (e.g., for three global functional states: wakefulness, sleep, and uncertain state, *K*=3), the *J* different objects must be related to *K* functional states.

The algorithm starts with *K* random clusters and then moves objects between those clusters in order to split objects into clusters such that variance in each cluster would be minimal, while variance between clusters would be maximal. This can be realized by minimization of the so-called cost function (Schreiber and Schmitz 1997). To implement this function, a measure of dissimilarity between objects must be obtained. This can be, for instance, determined by calculating Euclidean distances between objects in a multidimensional space. Figure C.13 shows a sketch of average dissimilarity of object *j* to cluster *k* (distance between *j* and *k*) and average dissimilarity within cluster *k*. The optimization strategy to determine the absolute minimum of the cost function will employ simulated annealing (Kirkpatrick, Gelatt, and Vecchi 1983; Press et al. n.d.), which follows local gradients, but can move against the gradient in order to escape "local minima" shadowing an absolute minima.

The algorithm described above works well under the assumption that the correct dissimilarity has been determined. For time series objects, in the simplest case, neuronal firing rates can be used as coordinates in a multidimensional space. However, application of this measure is rigid (although it has its own advantages), as it takes into account only local oscillatory properties. Another useful procedure will be the dissimilarity matrix calculation introduced (Schreiber and Schmitz 1997) based on the Grassberger-Procaccia cross-correlation sum (Grassberger and Procaccia 1983).

The classification algorithm given here may be referred to as unsupervised. It is based on the hypothesis of a "good" dissimilarity measure and does not include any optimization. This approach can be upgraded to a supervised training data set, where the correct results of classification are known *a priori* for a part of data and may be

used as a feedback for improvement of computational speed and reliability. However, even after tuning, the algorithm may fail, since brain plasticity may occur. Thus, the possibility of sudden mistakes may be corrected by means of the feedback.

The basic problem here is the nonstationary nature of brain function. This seems at first glance to be a big obstacle for any time series analysis. However, a detailed study of the problem indicates two features: First, all functional states are temporal and have essentially different time scales. For example, being awake can last for hours, while cognition can be as short as tens of milliseconds. Second, we may assume that only a limited number of functional states can coexist. These two features allow building a new adaptive algorithm capable of discriminating, in principle, any possible functional states.

There are three main parameters at play. The first is length of the time window, *T*; the next is the number of clusters of objects, *K*, being separated; and the third is a dissimilarity measurement. We can start the process of classification with relatively long *T* and small *K*. Thus, fast processes (functional states) would be eliminated due to averaging over a protracted time. Moreover, functional states with intermediate time scales and with a strong influence onto others would be left out due to very rough classification, since we have split patterns into a few clusters only. Then, when a first approximation of cluster boundaries is determined and it can reliably detect functional states of the top level, a step down can be taken by decreasing window size *T* and by including finer functional states (increasing *K*). Moreover, it is possible to work "within" a functional state of the upper level and reject all non-fitting. Such modification of the algorithm allows scalability and a method of exploration of all possible functional states. One problem here is that the deeper we go into the functional state hierarchy, the heavier the computation needed. However, the main parts of the algorithm can be easily paralleled and hence effectively performed by parallel computers or even by specially designed electronics.

Conclusions

We proposed that a novel brain-machine interface is realizable that would allow a robust solution to this important problem. This hardware/software approach allows a direct brain interface and the classification of its functional states using a benign invasive approach. We propose that this approach would be very helpful in human capacity augmentation and will yield significant new information regarding normal and abnormal brain function. Because its development and utilization is inevitable given the extraordinarily attractive feature of being retrievable, in the sense that the recording/stimulating filaments are small enough that the device can be removed without violating the integrity of the brain parenchyma.

Because such interfaces will probably be streamlined over the coming years in efforts such as "hypervision" (Llinás and Vorontsov in preparation), two-way direct human communication, and man-machine telepresence (which would allow actuator-based distant manipulation), this approach should be fully examined. Finally, the development of new nanotechnology instrumentation may ultimately be an important tool in preventive medicine and in diagnostic/therapeutic outcome monitoring of physiological parameters.

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HUMAN-MACHINE INTERACTION: POTENTIAL IMPACT OF NANOTECHOLOGY IN THE DESIGN OF NEUROPROSTHETIC DEVICES AIMED AT RESTORING OR AUGMENTING HUMAN PERFORMANCE

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Throughout history, the introduction of new technologies has significantly impacted human life in many different ways. Until now, however, each new artificial device or tool designed to enhance human motor, sensory, or cognitive capabilities has relied on explicit human motor behaviors (e.g., hand, finger, foot movements), often augmented by automation, in order to translate the subject's intent into concrete goals or final products. The increasing use of computers in our daily lives provides a clear example of such a trend. In less than three decades, digital computers have permeated almost every aspect of our daily routine and, as a result, have considerably increased human capabilities. Yet, realization of the full potential of the "digital revolution" has been hindered by its reliance on low-bandwidth and relatively slow user-machine interfaces (e.g., keyboard, mice, etc.). Indeed, because these user-machine interfaces are far removed from the way one's brain normally interacts with the surrounding environment, the classical Von Neuman design of digital computers is destined to be perceived by the operator just as another external tool, one that needs to be manipulated as an independent extension of one's body in order to achieve the desired goal. In other words, the reach of such a tool is limited by its inherent inability to be assimilated by the brain's multiple internal representations as a continuous extension of our body appendices or sensory organs. This is a significant point, because in theory, if such devices could be incorporated into "neural space" as extensions of our muscles or senses, they could lead to unprecedented (and currently unattainable) augmentation in human sensory, motor, and cognitive performance

It is clear that recent advances in nanotechnology could significantly impact the development of brain-machine interfaces and neuroprosthetic devices. By establishing direct links between neuronal tissue and machines, these devices could significantly enhance our ability to use voluntary neuronal activity to directly control mechanical, electronic, and even virtual objects as if they were extensions of our own bodies.

Main Goals

For the past few years, we and others have proposed that a new generation of tools can be developed in the next few decades in which direct brain-machine interfaces (BMIs) will be used to allow subjects to interact seamlessly with a variety of actuators and sensory devices through the expression of their voluntary brain activity. In fact, recent animal research on BMIs has supported the contention that we are at the brink of a technological revolution, where artificial devices may be "integrated" in the multiple sensory, motor, and cognitive representations that exist in the primate brain. Such a demonstration would lead to the introduction of a new generation of actuators/sensors that can be manipulated and controlled through direct brain processes in virtually the same way that we see, walk, or grab an object.

At the core of this new technology is our growing ability to use electrophysiological methods to extract information about intentional brain processes (e.g., moving an arm) from the raw electrical activity of large populations of single neurons, and then translate these neural signals into models that control external devices. Moreover, by providing ways to deliver sensory (e.g., visual, tactile, auditory, etc.) feedback from these devices to the brain, it would be possible to establish a reciprocal (and more biologically plausible) interaction between large neural circuits and machines and hence fulfill the requirements for artificial actuators of significantly augmenting human motor performance to be recognized as simple extensions of our bodies. Using this premise and taking advantage of recent developments in the field of nanotechnology, one can envision the construction of a set of closed-loop control BMIs capable of restoring or augmenting motor performance in macro, micron, and even nano environments (Fig. C.14).

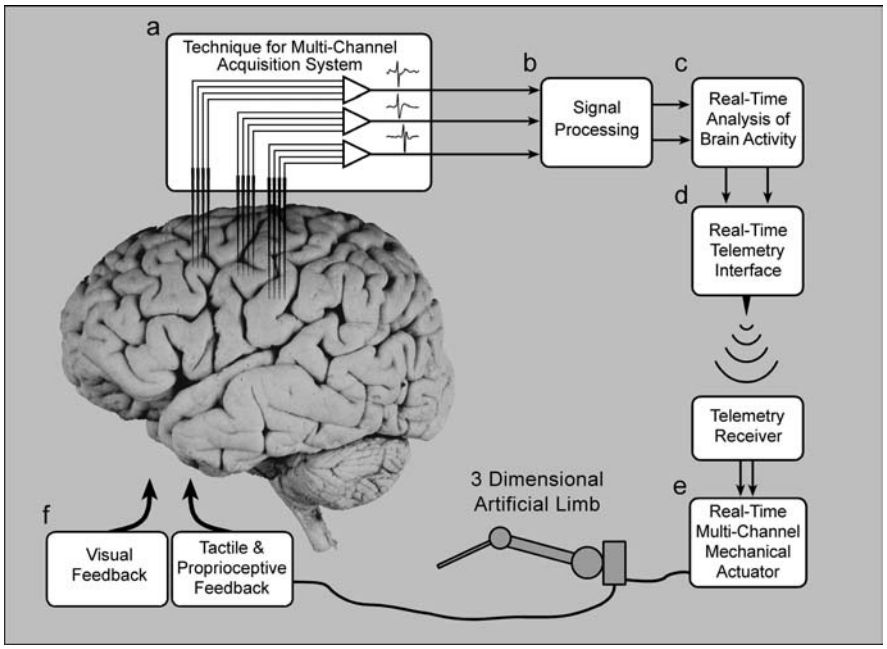

Figure C.14. General architecture of a closed-loop control brain-machine interface: Neuroprosthesis for restoring motor function of damaged brain areas.

Envisioned Utility of BMIs

The full extent to which BMIs would impact human behavior is vastly unknown. Yet, short-term possibilities are innumerable. For example, there is a growing consensus that BMIs could provide the only viable short-term therapeutic alternative to restore motor functions in patients suffering from extensive body paralysis (including lack of communication skills) resulting from devastating neurological disorders.

Assuming that noninvasive techniques to extract large-scale brain activity with enough spatial and temporal resolution can be implemented, BMIs could also lead to a major paradigm shift in the way normal healthy subjects can interact with their environment. Indeed, one can envision a series of applications that may lead to unprecedented ability to augment perception and performance in almost all human activities. These applications would involve interactions with either real or virtual environments. According to this view, real environments can also include local or remote control relative to the human subject, while virtual environments can be realistic or intentionally unrealistic. Here are some examples.

1. **Local, real environment:** Restoration of the motor function in a quadriplegic patient. Using a neurochip implanted in the subject's brain, neural signals from healthy motor brain areas can be used to control an exoskeletal or prosthetic robotic arm used to restore fundamental motor functions such as reaching, grabbing, and walking.
2. **Remote, real environment:** Superhuman performance, such as clearing heavy debris by a robot controlled by the brain signals of a human operator located far away from the danger zone. Recent results by the P.I. and his collaborators have demonstrated that such remote control could be achieved even across the Internet.
3. **Realistic virtual environment:** Training to learn a complex sequence of repair operations by the trainee's brain directly interacting with a virtual reality program, with or without the involvement of the trainee's peripheral sensorimotor system.
4. **Unrealistic virtual environment:** Experiencing unrealistic physics through a virtual reality system for a "what if" scenario, in order to understand deeply the consequences of terrestrial physics.

Given the significant degree of plasticity documented even in the adult brain, repeated use of BMIs will likely transform the brain itself, perhaps more rapidly and extensively than what is currently possible with traditional forms of learning. For example, if a robot located locally or remotely is repeatedly activated via a BMI, it is likely that cortical areas specifically devoted to representing the robot will emerge, causing the robot to effectively become an extra limb of the user.

What real advantages might we obtain from future BMI based devices, compared to more conventional interfaces such as joysticks, mice, keyboards, voice recognition systems, and so forth? Three possible application domains emerge:

1. *Scaling of position and motion*, so that a "slave" actuator, being controlled directly by the subject's voluntary brain activity, can operate within workspaces that are either far smaller (e.g., nanoscale) or far bigger (e.g., space robots; industrial robots, cranes, etc.) than our normal reach

2. *Scaling of forces and power*, so that extremely delicate (e.g., microsurgery) or high-force tasks (e.g., lifting and displacing a tank) can be accomplished
3. *Scaling of time*, so that tasks can be accomplished much more rapidly than normal human reaction time, and normally impossible tasks become possible (e.g., braking a vehicle to a stop after seeing brake lights ahead; catching a fly in your hand; catching something you have dropped; responding in hand-to-hand combat at a rate far exceeding that of an opponent)

To some extent, all these tasks, with the exception of time scaling, can, in principle, be accomplished though conventional teleoperator systems in which the human using his limbs operates a master device, which, in turn, controls a local or remote slave device. There is a history of five decades of research in this area of robotics, with moderate success, such as recent commercial development of teleoperated surgical systems. Major difficulties have been the design of appropriate master devices that the human can interact with naturally and the destabilizing effects of long time delay between the master and the slave. BMIs offer unique advantages in two ways:

1. They eliminate the need for master devices that interact with the human
2. Since the human is directly operating through his brain, the time delays associated with the signal transmission from the peripheral sensors to the CNS (~ 10–30 msec) and from CNS to the muscles (~10-30 msec), and then the time required of a limb to complete the needed action (~100-900 msec), can be reduced by an order of magnitude.

Elimination of the need for a master device is a radical departure from conventional teleoperation. Furthermore, the reduction of time delays leads to the exciting possibility of superhuman performance. For example, moving an arm from point A to point B can take ~500 msec from the time muscles are commanded by the brain, because of the force generation limitations of the muscles, the inertia of the arm, and the need to accelerate from A and to decelerate to B. But if a slave robot that is much better than the human arm in terms of power/mass ratio is directly controlled though a BMI, all three types of time delays (peripheral sensory, motor signal transmission, and limb motion) can be minimized or eliminated, possibly leading to faster and more stable operation of the slave robot. For instance, it is possible for an impaired or unimpaired person to wear an arm exoskeleton that directly interacts with the brain much faster than the natural arms.

In recent years, work developed by our laboratories has demonstrated the feasibility of building BMIs dedicated to the task of utilizing brain-derived signals to control the 1-D and 3-D movements of artificial devices. In a series of studies, we have provided the first demonstrations in animals that such BMIs can be built, that animals can learn to operate these devices in order to obtain a reward, and that motor control signals derived from the extracellular activity of relatively small populations of cortical neurons (50-100 cells) can be used to reproduce complex 3-D arm movements in a robotic device in real time.

Recent advances in nanotechnology could help significantly the advance of this area of research. First, this technology could provide new ways to extract large-scale brain activity by reducing the degree of invasiveness of current electrophysiological methods. Investment in research aimed at designing a new generation of VLSI

aimed at both conditioning and analyzing large-scale electrical brain activity will also be required. Finally, a complete new generation of actuators, designed to operate in micro- or nanospaces needs to be built, since there are many new applications that can be envisioned if brain-derived signals can be employed to directly control nanomachines.

NANOTECHNOLOGY: THE MERGING OF DIAGNOSTICS AND TREATMENT

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The key to advancing from the discovery stage of nanoscience to commercially feasible nanotechnology is the ability to reliably manufacture nanoscale features and control nanoscale functions. The application of nanotechnology to biology further requires the functional nano-interface between artificial and biological components. From a systems perspective, this requires signal transduction at matching impedances so that sensitivity and specificity are adequate to decipher the biological events. The maturation of these capabilities will enable the probing and manipulating of the fundamental building blocks of biology, namely biomolecules such as carbohydrates, lipids, nucleic acids, and proteins.

The biological cell has proven to be the most intricate functional system of its scale. Unique functionalities include its ability to regulate and adapt, hierarchical self-assembly, repair and maintenance, parallel processing, just-in-time processes, asynchronous control and signaling, and scalability from nano to macro. However, these features and functions are hard to quantify, model, engineer, and reprogram. On the other hand, microfabrication and nanofabrication techniques have given us integrated nanoscale electronics, microfluidics, microelectromechanical systems (MEMS), and microphotonics. These top-down fabrication techniques allow addressability of large-scale component platforms. On the other hand, bottom-up nanofabrication techniques (such as self-assembly) mimic how biology builds very complex systems out of simple molecules. As the scale of these two fields overlaps, devices can be developed with high sensitivity and selectivity for detecting and interfacing to biomolecules.

Projects exemplifying the field of nanobiotechnology include single molecule detection studies, functional imaging of cells and biomolecules by scanning probe microscopy, nanoparticles for targeted therapy, nanomechnical devices to measure biomolecular force interactions, etc. These research efforts represent the start towards interfacing with biological functions at the most fundamental level. However, biology is the intertwined combination of many single molecular events, each being coupled with one another either synchronously or asynchronously. To truly unveil biological events such as cell signaling pathways, genetic mutation processes, or the immune responses to pathogens, one must have a method to generate large-scale, multifunctional nano-bio interfaces with readout and control at the single biomolecule level.

I provide three visions for features of the nanobiotechnology roadmap:

1. The development of a “biological microprocessor” for synthesizing and analyzing biomolecules on nano platforms (liposomes, nanoparticles, self-assembled monolayers, and membranes) in fluids. These “biomolecular

nanotransducers" will be able to function (1) as multiplexed nanomedicines capable of long duration, *in vivo* targeted detection, diagnosis, and treatment of molecular diseases; (2) as key ingredients of smart coatings for versatile environmental monitoring of toxins/pathogens; and (3) as engineered biomolecular nanosystems that mimic cellular functions for fundamental biology experiments.

2. The coupling of biomolecular units — whether they be DNA, receptors, antibodies, or enzymes — with MEMS for reassembling cell components and reprogramming cell functions. This will enable the rewiring of biological cell pathways in artificially controlled platforms such that it will be possible to carry out preclinical experiments without the use of animals or humans.
3. The coupling of "nano guards for health" (e.g., nanoparticles) with microfluidic controllers for long-term control of certain health parameters. For instance, the feedback loop of a glucose sensor and delivery of nano artificial islets can enable the merging of detection, diagnosis, and treatment into one MEMS device.

ARTIFICIAL BRAINS AND NATURAL INTELLIGENCE

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It is widely accepted that nanotechnology will help push Moore's Law to, or past, its prediction that the next few decades will witness a truly amazing advance in affordable personal computing power. Several visionary techno-futurists have attempted to estimate the equivalent power of the human brain to predict when our handheld personal computers may be able to convince us that they occasionally feel, well, unappreciated, at least. With the advent of nano-neuro-techniques, neuroscience is also about to gain unfathomable insight into the dynamical mechanisms of higher brain functions. But many neuroscientists who have dared to map the future path to an artificial brain with human intelligence do not see this problem in simple terms of "computing power" or calculations per second. We agree that the near future of nano-neuro-technology will open paths to the development of artificial brains with natural intelligence. But we see this future more in terms of a coming nano-neuro-cogno-symbiosis that will enhance human potential in two fundamental ways: (1) by creating brilliant, autonomous artificial partners to join us in our struggle to improve our world and (2) by opening direct channels of natural communication between human and artificial nervous systems for the seamless fusion of technology and mind.

Human brain function emerges from a complex network of many billion cooperating neurons whose activity is generated by nanoscale circuit elements. In other words, the brain is a massively parallel nanocomputer. And, for the first time, nanotechnology reveals approaches toward the design and construction of computational systems based more precisely upon the natural principles of nervous systems. These natural principles include (1) enormous numbers of elementary nonlinear computational components, (2) extensive and interwoven networks of modifiable connectivity patterns, (3) neurointeractive sensory/motor behavior, and (4) a long period of nurtured development (real or virtual). We believe human-like

functions will likewise emerge from artificial brains based upon these natural principles.

A simple nanoelectronic component, the resonant tunneling diode, possesses nonlinear characteristics similar to the channel proteins that are responsible for much of our neurons' complex behavior. In many ways, nanoscale electronics may be more suitable for the design of nonlinear neural networks than as simple switching elements in digital circuits. At this NBIC meeting, Phil Kuekes from Hewlett-Packard described a nanoscale cross-link connection scheme that may provide an approach to solving the truly difficult problem of how to interconnect enormous networks of these nanocomponents. But as a beginning, these initial steps to realization of a nano-neuro-computer permit consideration of the much greater density that is possible using nanoelectronic neurons than has so far been possible with microelectronic solutions, where equivalent chip architectures would need to be millions of times larger. If the size of the artificial brain were small enough to mount on a human-size organism, then it might be simpler to design nurturing environments to promote the emergence of human-like higher functions.

Decades of neuroscience progress have shed much light upon the complexity of our brain's functional neuro-architecture (e.g., Felleman and Van Essen 1991). Despite its extreme complexity (>100,000 miles of neuron fibers), fundamental principles of organization have been established that permit a comprehensive, although highly simplified sketch of the structure responsible for natural intelligence. In addition, neuroscience has characterized many of the principles by which the network's connections are constantly changing and self-organizing throughout a lifetime of experience (e.g., Abbott and Nelson 2001). While some futurists have included the possibility that it will be possible to exactly replicate the cellular structure of the human brain (Kurzweil 1999), it seems impossible from a neuroscience point of view, even with nanotechnology. But it is not necessary to be too precise. Genetics is not that precise. We know many of the principles of neuro-competition and plasticity that are the basis for the continuous refinement of neural functions in the midst of precise wiring and environmental complexity. But the only test of these far-reaching principles is to construct a working model and learn to use it.

Constrained by the limits of microtechnology, previous attempts to mimic human brain functions have dealt with the brain's extreme complexity using mathematical simplifications (i.e. neural networks) or by careful analysis of intelligent behavior (i.e. artificial intelligence). By opening doors to the design and construction of realistic brain-scale architectures, nanotechnology is allowing us to rethink approaches to human-like brain function without eliminating the very complexity that makes it possible in the first place. The tools of nonlinear dynamical mechanics provide the most suitable framework to describe and manage this extreme complexity (e.g. Kelso 1995; Freeman 2000). But the first step is to recognize and accept the natural reality that the collective dynamics of the neural process responsible for the highest human functions are not mathematically tractable.

Instead, higher functions of the brain are emergent properties of its neuro-interactivity between neurons, between collections of neurons, and between the brain and the environment. While purely deterministic, it is no more possible to track the cause-effect path from neuron activity to higher functions such as language

and discovery than it is to track the path from an H_2O molecule to the curl of a beach wave. Unfortunately, appeals to emergence always leave an unsatisfying gap in any attempt to provide a complete explanation, but nature is full of examples, and classical descriptions of human intelligence have depended strongly upon the concept of emergence (i.e. Jean Piaget, see Elman et al. 1997). But modern emergent doctrine is gaining legitimacy from the powerful new tools of nonlinear dynamical mathematics for the analysis of fractals and deterministic chaos. Instead of tracking cause-effect sequence, the new paradigm helps to identify the dynamical mechanisms responsible for the phase shifts from water to ice, or from exploring to understanding.

From the perspective of neuro-interactive emergence, brain function is entirely self-organized so it may only be interpreted with respect to the interactive behavior of the organism within meaningful contexts. For instance, speech communication develops by first listening to one's own speech sounds, learning to predict the sensory consequence of vocalization, and then extending those predictions to include the response of other speakers to one's own speech. This natural process of self-growth is radically different from the approaches taken by artificial intelligence and "neural net" technologies. The kernel of this natural process is a proactive hypothesis-testing cycle spanning the scales of the nervous system that acts first and learns to predict the resulting consequences of each action within its context (Cauller, in press; see also Edelman and Tonomi 2001). Higher functions of children emerge as a result of mentored development within nurturing environments. And emergence of higher functions in artificial brains will probably require the same kinds of care and nurturing infrastructure we must give our children.

So the future of the most extreme forms of machine intelligence from this neuroscience perspective differs in many respects from popular visions: (1) "artificial people" will be very human-like given that their natural intelligence will develop within the human environment over a long course of close relationships with humans; (2) artificial people will not be like computers any more than humans are. In other words, they will not be programmable or especially good at computing. And (3) artificial people will need social systems to develop their ethics and aesthetics.

An optimal solution to the problem of creating a seamless fusion of brain and machine also needs to be based upon these neurointeractive principles. Again, nanotechnology, such as minimally invasive nano-neuro transceivers, is providing potential solutions to bridge the communication gap between brain and machine. But the nature of that communication should be based upon the same neural fundamentals that would go into the design of an artificial brain.

For instance, sensory systems cannot be enhanced by simply mapping inputs into the brain (e.g., stimulating the visual cortex with outputs from an infrared camera won't work). The system must be fused with the reciprocating neurointeractivity that is responsible for ongoing conscious awareness. This means that brain control over the sensory input device is essential for the system to interpret the input in the form of natural awareness (e.g., there must be direct brain control over the position of the video source). In other words, brain enhancements will involve the externalization of the neurointeractive process into peripheral systems that will respond directly to brain signals. These systems will become an extension of the

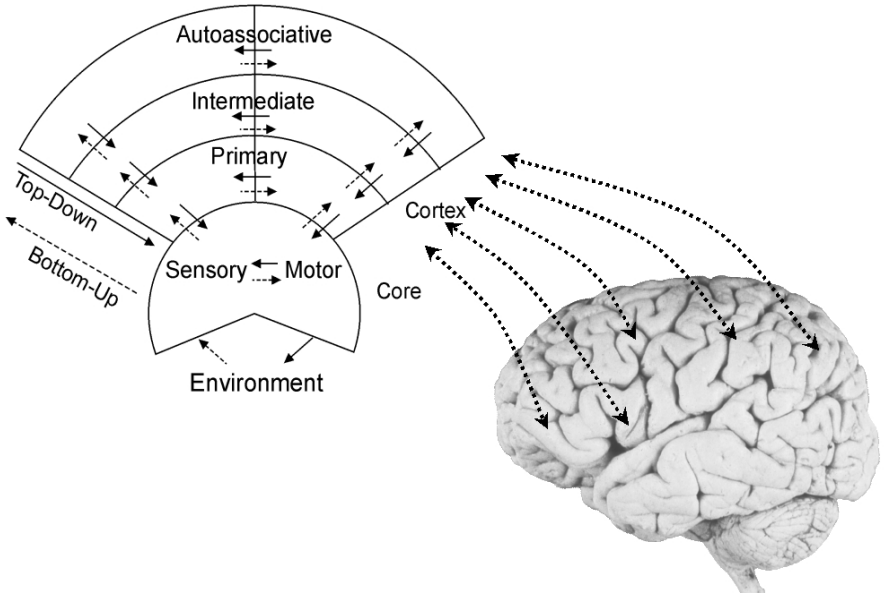

Figure C.15. Neurointeractive artificial brain/human brain interface for neuroprosthesis or enhancement.

human mind/body over a course of accommodation that resembles the struggle of physical therapy following cerebral stroke.

Fusion of artificial brains into larger brains that share experience is a direct extension of this line of reasoning. This also would not be an immediate effect of interconnection, and the fusion would involve give and take on both sides of the connection over an extended course of active accommodation. But the result should surpass the sum of its parts with respect to its ability to cope with increasing environmental complexity.

Speculation leads to the next level of interconnection, between human and artificial brains. On the face of it, this appears to be a potential path to cognitive enhancement. However, the give and take that makes neurointeractive processes work may be too risky when humans are asked to participate.

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CONVERGING TECHNOLOGIES FOR PHYSIOLOGICAL SELF-REGULATION

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The biofeedback training method is an effective health-enhancement technique, which exemplifies the integration of biotechnology and information technology with the reinforcement principles of cognitive science. Adding nanotechnology to this mix will enable researchers to explore the extent to which physiological self-regulation can be made more specific and even molecular, and it may lead to a entire new class of effective health-enhancing and health-optimizing technologies.

Vision

Physiological Self-Regulation Training

Biofeedback is a well-established and scientifically validated method to treat a variety of health problems and normalize or enhance human physiological functioning. It consists of placing sensors on the body to measure biological activity and enabling patients to self-correct their physiological activity by showing them on a computer screen (typically in the form of dynamic graphs) what is going on inside their bodies.

> Biofeedback means "the feeding back of information to the individual about change in a physiological system." It implies that the subject is continuously, or discontinuously, informed about change in a particular physiological system under study. The information is believed to act as a reinforcer for further changes in either the same or the opposite direction. As a result of instrumental learning, a physiological response may come under "instructional" or "volitional" control as a function of the feedback of information. (Hugdahl 1995, 39)

When patients are able to observe the moment-to-moment changes in their physiological activity in this way, they can learn over time to control various body functions that are usually beyond conscious control, such as heart rate, muscle tension, or blood flow in the skin:

> According to a basic premise in biofeedback applications, if an individual is given information about biological processes, and changes in their level, then the person can learn to regulate this activity. Therefore, with appropriate conditioning and training techniques, an individual can presumably learn to control body processes that were long considered to be automatic and not subject to voluntary regulation. (Andreassi 2000, 365)

Biofeedback has been used for 40 years with considerable success in the treatment of various health problems, such as migraine headaches, hypertension, and muscle aches and pains. More recently, biofeedback training has been used to enhance performance in a number of occupations and sports activities (Norris and Currieri 1999). At NASA Langley Research Center, work in physiological self-regulation is directed at reducing human error in aviation:

> Our work has focused on a number of areas with the goal of improving cognitive resource management, including that of physiological self-regulation reported here. Other areas include adaptive task allocation, adaptive interfaces, hazardous unawareness modeling, cognitive awareness training, and stress-counter-response training. (Prinzel, Pope, and Freeman 2002, p. 196)

Intrasomatic Biofeedback: A New Frontier

The exclusive reliance upon sensing physiological functions from the surface of the body has limited biofeedback's specificity in targeting the physiological processes that underlie human performance and the physiological dysregulation implicated in several disorders. Biofeedback technology has yet to incorporate recent advances in biotechnology, including nanoscale biosensors, perhaps because biofeedback research and practice is dominated by a focus on traditional and proven training protocols rather than on biotechnology.

> As a result of the development of new analytical tools capable of probing the world of the nanometer, it is becoming increasingly possible to characterize the chemical and mechanical properties of cells (including processes such as cell division and locomotion) and to measure properties of single molecules. These capabilities complement (and largely supplant) the ensemble average techniques presently used in the life sciences. (Roco and Bainbridge 2001, 7)

Current biofeedback technology still mostly detects, processes, and feeds back to trainees broad signals from sensors on the skin. Such surface sensors are only suited for providing summary information about broad functional characteristics of the organism, like overall autonomic functioning, summative brain activity in a large portion of the cortex, or activity levels of large masses of striated muscle.

Nanoscale technologies, specifically nanoscale biosensor technology, hold the potential for realtime sensing and feedback of internal bodily processes that are the origins or precursors of the physiological signals sensed on the skin surface by current biofeedback technology. Intrasomatic signals, closer to the physiological source of the body activity of interest than surface-detectable signals, could be used for more targeted and precise feedback conditioning of physiological functions and physiological dysregulation. They could also be used to dynamically feed back to patients the consequences and benefits of exercises and practices, or warnings of hazardous alterations in physiology, in order to provide education as well as motivation for adhering to prescribed behavioral treatment regimens. Furthermore, the presence of such small intrasomatic sensors could enable physicians or surveillance computers to titrate or fine-tune the treatment of a patient's disorder (such as medication flow-rate) in ways otherwise not possible.

Early work by Hefferline, Keenan, and Harford (1959) demonstrated that covert physiological responses could be conditioned by attaching consequences, in a traditional psychological reinforcement paradigm, to the production of the responses without the trainee's conscious, deliberate effort to control the responses. Most biofeedback training successes do indeed operate without the necessity for the trainee to be able to articulate the exact nature of the efforts they employ in the learning process, and sometimes without their even trying to consciously control the process. Nevertheless, an additional application of feedback of nanoscale biosensed parameters may be to inform the trainee of the results of his/her overt efforts to facilitate management of a physiological function. An example would be the moment-to-moment feedback of blood oxygenation level or oxygen/CO_2 balance in respiration training for hyperventilation in panic disorder (Ley 1987).

Roles of Converging Technologies

The roles of NBIC technologies in the intrasomatic biofeedback vision are illustrated schematically in Figure C.16.

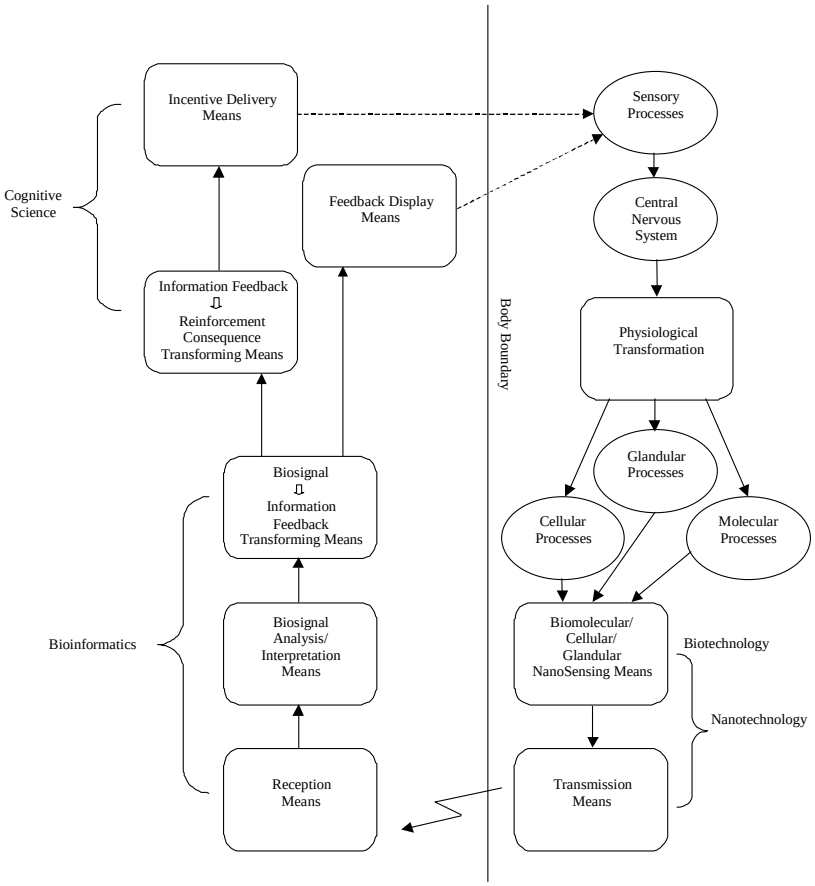

Figure C.16. Intrasomatic biofeedback

Cognitive Science

> Mainly used in psychophysiology as an applied technique, the principle of biofeedback goes back to the idea that nonvolitional, autonomic behavior can be instrumentally conditioned in a stimulus-reinforcement paradigm.
>
> Traditional learning theory at the time of the discovery of the biofeedback principle held that an autonomic, involuntary response could be conditioned only through the principles of classical, or Pavlovian, conditioning. Instrumental, operant learning could be applied only to voluntary behavior and responses. However, in a series of experiments, Miller (1969) showed that autonomic behavior, like changes in blood pressure, could be operantly conditioned in rats (Hugdahl 1995, 40).

In the beginning of the biofeedback field, researchers, working with animals, experimented with more precisely accessing internal physiological phenomena to provide the signals and information representing the functions to be conditioned:

> The experimental work on animals has developed a powerful technique for using instrumental learning to modify glandular and visceral responses. The improved training technique consists of moment-to-moment recording of the visceral function and immediate reward, at first, of very small changes in the desired direction and then of progressively larger ones. The success of this technique suggests that it should be able to produce therapeutic changes (Miller 1969, 443-444).

Miller identified critical characteristics that make a symptom (or physiological function) amenable to instrumental conditioning through biofeedback:

> Such a procedure should be well worth trying on any symptom, functional or organic, that is under neural control, that can be continuously monitored by modern instrumentation, and for which a given direction of change is clearly indicated medically — for example, cardiac arrhythmias, spastic colitis, asthma, and those cases of high blood pressure that are not essential compensation for kidney damage (Miller 1969, 443-444).

The mechanism of neural control that would enable instrumental conditioning of basic molecular physiological processes has yet to be identified. Current understanding is limited to the notion that it generally involves a “bucket brigade” effect where willful cognitive influences in the cortex are handed down through the limbic system and on down into the hypothalamus, which disseminates the effect throughout the body via various neural and endocrine avenues.

Similarly, researchers in the field of psychoneuroimmunology have yet to find the exact biological mechanisms linking the brain and the immune system. Nevertheless, Robert Ader, one of the first to present evidence that immune responses could be modified by classical conditioning (Ader and Cohen 1975), states:

> There are many psychological phenomena, and medical phenomena for that matter, for which we have not yet defined the precise mechanisms. It doesn't mean it's not a real phenomenon (Azar 1999).

Nanobiotechnology

Miller's (1969, 443-444) requirement that the physiological function be "continuously monitored by modern instrumentation" is now made possible by nanoscale biosensors, enabling the investigation of the instrumental conditioning of biomolecular phenomena.

> Implantable sensors or "smart" patches will be developed that can monitor patients who are at risk for specific conditions. Such sensors might monitor, for example, blood chemistry, local electric signals, or pressures. The sensors would communicate with devices outside the body to report results, such as early signals that a tumor, heart damage, or infection is developing. Or these sensors could be incorporated into "closed loop" systems that would dispense a drug or other agent that would counteract the detected anomaly. For chronic conditions like diabetes, this would constitute a great leap forward. Nanotechnology will contribute critical technologies needed to make possible the development of these sensors and dispensers (NSTC 2000, 54, 55).

Another "closed loop system" that would "counteract the detected anomaly" is intrasomatic biofeedback training. In this case, remediation of a physiological anomaly or suboptimal condition would be achieved by self-regulation learned through instrumental conditioning, rather than by an external agent such as a drug or nanodevice.

Freitas (1999, section 4.1) describes "nanosensors that allow for medical nanodevices to monitor environmental states at three different operational levels," including "local and global somatic states (inside the human body)," and cellular bioscanning:

> The goal of cellular bioscanning is the noninvasive and non-destructive *in vivo* examination of interior biological structures. One of the most common nanomedical sensor tasks is the scanning of cellular and subcellular structures. Such tasks may include localization and examination of cytoplasmic and nuclear membranes, as well as the identification and diagnostic measurement of cellular contents including organelles and other natural molecular devices, cytoskeletal structures, biochemical composition, and the kinetics of the cytoplasm (Freitas 1999, section 4.8).

The function of "communicating outside the body to report results" (NSTC 2000, 54, 55) is essential for an intrasomatic biofeedback application. Freitas (1999) describes a similar function for nanorobots:

> In many applications, *in vivo* medical nanodevices may need to communicate information directly to the user or patient. This capability is crucial in providing feedback to establish stable and reliable autogenous command and control systems (Chapter 12).

> Outmessaging from nanorobot to the patient or user requires the nanodevice to manipulate a sensory channel that is consciously available to human perception, which manipulation can then be properly interpreted by the patient as a message.
>
> Sensory channels available for such communication include sight, audition, gustation and olfaction, kinesthesia, and somesthetic sensory channels such as pressure, pain, and temperature (Freitas 1999, section 7.4.6).

In this application, "outmessaging" is described as enabling user control of a nanorobot; for intrasomatic biofeedback, this function would provide the information that acts as a reinforcer for conditioning changes in cellular and molecular processes (Figure C.16).

Transforming Strategy

A Technical Challenge

Early on, Kamiya (1971) specified the requirements for the biofeedback training technique, and these have not changed substantially:

- The targeted physiological function must be monitored in real time.
- Information about the function must be presented to the trainee so that the trainee perceives changes in the parameter immediately.
- The feedback information should also serve to motivate the trainee to attend to the training task.

The challenges for the fields of nanotechnology, biotechnology, information technology, and cognitive science (NBIC) in creating the technology to enable internally targeted physiological self-regulation technology can be differentiated according to the disparities between (1) the time response of existing physiometric technology, (2) the time course of the targeted physiological processes, and (3) the requirements for feedback immediacy in the biofeedback paradigm. Realtime sensing is essential to make the processes available for display and attaching sensory feedback consequences to detected changes.

The physiological processes most readily amenable to biofeedback self-regulation are those where the internal training targets are available in real time with current or emerging technologies, such as electrical (e.g. brainwave) and hydraulic (e.g. blood flow) physiological signals.

Instruments using microdialysis, microflow, and biosensor technologies to deliver blood chemistry data such as glucose and lactate in real time (European Commission 2001) will need to reduce test cycle time from minutes to seconds to meet the feedback immediacy criterion required for biofeedback training. Even then, it may be discovered that time delays between the initiation of the production of these chemicals and their appearance in the bloodstream require that signals from upstream stages in the formation process are more appropriate targets for feedback in the self-regulation training loop.

Flow cytometry is an example of an offline, non-realtime technology, in this case for measuring certain physical and chemical characteristics, such as size, shape, and internal complexity, of cells or particles as they travel in suspension one by one past

a sensing point. For the blood cell formation process that controls these characteristics of cells, hematopoiesis, to become a candidate for physiological self-regulation training will require advances in molecular-scale technology. These advances will probably need to occur in the upstream monitoring of molecular or biosignal (hormonal, antibody, etc.) precursors of the blood cell formation process, bringing tracking of the process into the realtime scale required for feedback immediacy.

Internal nanosensors will similarly solve the time-response problem that has prevented the utilization of brain functional monitoring and imaging in biofeedback.

> Thus, current functional imaging methods are not in real time with brain activity; they are too slow by a factor of 100 or more. The big advance will be to develop functional imaging techniques that show us — as it is happening — how various areas of the brain interact. … Do not ask me what the basis of this new imaging will be. A combination of electrical recording and changes in some other brain properties perhaps? (McKhann 2001, 90)

> The precision and speed of medical nanodevices is so great that they can provide a surfeit of detailed diagnostic information well beyond that which is normally needed in classical medicine for a complete analysis of somatic status (Freitas 1999, section 4.8).

Enabling Collaborations

The collaboration of key institutions will be necessary to expedite the development of the intrasomatic biofeedback vision. Potentially enabling joint efforts are already in place (National Aeronautics and Space Administration [NASA] and the National Cancer Institute [NCI] 2002):

> NASA and the National Cancer Institute (NCI) cosponsor a new joint research program entitled "Fundamental Technologies for the Development of Biomolecular Sensors." The goal of this program is to develop biomolecular sensors that will revolutionize the practice of medicine on Earth and in space.

> The Biomolecular Systems Research Program (BSRP) administrates the NASA element of the new program, while the Unconventional Innovations Program (UIP) does so for NCI.

> NASA and NCI are jointly seeking innovations in fundamental technologies that will support the development of minimally invasive biomolecular sensor systems that can measure, analyze, and manipulate molecular processes in the living body. (National Aeronautics and Space Administration [NASA] 2002)

One of the purposes that this program is designed to serve is NASA's requirement "for diagnosis and treatment of injury, illness, and emerging pathologies in astronauts during long duration space missions … Breakthrough technology is needed to move clinical care from the ground to the venue of long duration space flight … Thus, the space flight clinical care system must be autonomous …" (NASA/NCI 2001). Intrasomatic biofeedback's potential for self-

remediation of physiological changes that threaten health or performance would be useful in many remote settings.

The nanotechnology, biotechnology, and information technology (NBI) components of the NASA/NCI joint project are specified in a NASA News Release:

> The ability to identify changes such as protein expression or gene expression that will develop into cancer at a later date may enable scientists to develop therapies to attack these cells before the disease spreads. "With molecular technologies, we may be able to understand the molecular signatures within a cell using the fusion of biotechnology, nanotechnology, and information technology," [John] Hines [NASA Biomolecular Physics and Chemistry Program Manager] said.
>
> [NASA] Ames [Research Center] will focus on six key areas in molecular and cellular biology and associated technologies. Biomolecular sensors may some day be able to kill tumor cells or provide targeted delivery of medication. Molecular imaging may help scientists understand how genes are expressed and how they control cells. Developments in signal amplification could make monitoring and measurement of target molecules easier. Biosignatures — identification of signatures of life — offer the possibility of distinguishing cancerous cells from healthy cells. Information processing (bioinformatics) will use pattern recognition and modeling of biological behavior and processes to assess physiological conditions. Finally, molecular-based sensors and instrumentation systems will provide an invaluable aid to meeting NASA and NCI objectives (Hutchison 2001).

The NASA/NCI project is designed to "develop and study nanoscale (one-billionth of a meter) biomedical sensors that can detect changes at the cellular and molecular level and communicate irregularities to a device outside the body" (Brown 2001). This communication aspect of the technology will make possible the external sensory display of internal functioning that is essential to the intrasomatic biofeedback vision (Figure C.16).

Collaborations such as this NASA/NCI project provide the NBI components of the intrasomatic biofeedback vision. The participation of organizations devoted to the development and application of cognitive science (C), such as those specified in Figure C.17, would complete the set of disciplines necessary to realize the vision.

Estimated Implications: The Promise of Intrasomatic Biofeedback

It has not been widely appreciated outside the highly insular field of psychophysiology that humans, given sufficiently informative feedback about their own physiological processes, have both the capacity and inherent inclination to learn to regulate those processes. This phenomenon has, however, been established conclusively in numerous biofeedback applications across a range of different biological functions, including the training of brain electrical activity and of autonomic responses. The integration of NBIC technologies will enable the health- and performance-enhancing benefits of this powerful methodology to be extended to

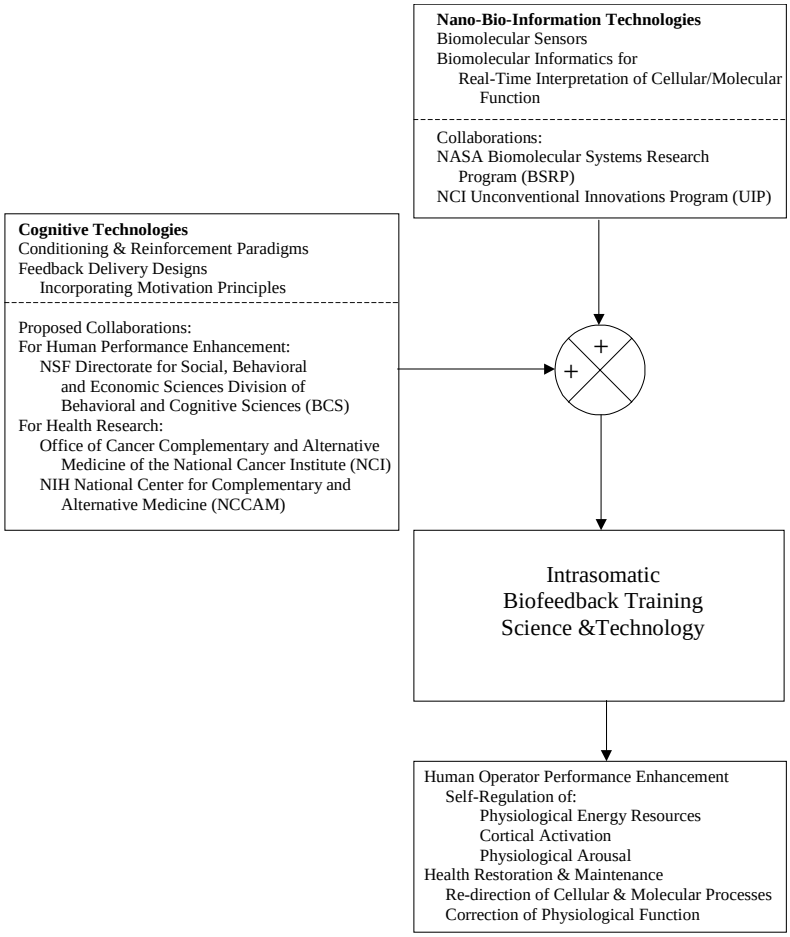

Figure C.17. Enabling collaborations.

other critical physiological processes not previously considered amenable to change by training.

While self-regulation of basic molecular physiological processes may seem fantastical at the present time, it is worth keeping in mind that therapeutic conditioning of autonomic and brainwave signals, now well established, was similarly considered in the fantasy realm no more than four decades ago. The discovery of the human capacity for physiological self-regulation awaited the inventiveness of pioneers, who, in a bold empowering stroke, displayed physiological signals, previously scrutinized only by the researcher, to the subjects whose signals they were, with the aim of giving the subjects control of these processes. This innovation began the discovery process that has demonstrated that, given the right information about their bodily processes in the right form, people can exert impressive control over those responses. The integration of NBIC with the biofeedback method opens an entirely new frontier, inviting the pioneers of a new

era in psychophysiology to explore the extent to which this physiological self-regulation can be made more precise, perhaps even to the point of reliably modifying specific molecular events. These developments will enable human beings to willfully induce inside their own bodies small and highly specific biological changes with large health- and performance-enhancing consequences.

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IMPROVING QUALITY OF LIFE OF DISABLED PEOPLE USING CONVERGING TECHNOLOGIES

G. Wolbring, U. Calgary, and R. Golledge, UCSB

It is understood that NBIC should be used in a way that diminishes the discrimination against disabled people, advances their acceptance and integration into society, and increases their quality of life.

The Vision

1. NBIC has the potential to give disabled people, and this includes many elderly, the ability to choose between different modes of information output, whether visual, audio, print, or others, as all these modes can be offered routinely at the same time. It has the potential to change computer interface architecture so that disabled people, including those who are blind, sight-impaired, dyslexic, arthritic, immobile, and deaf, can access the Internet and its webpages as transparently and quickly as able-bodied people by means of, for example, holographic outputs; force-feedback, vibrotactile, vastly improved natural speech interfaces; and realtime close captioning. Multimodal access to data and representations will provide a cognitively and perceptually richer form of interaction for all persons, regardless of impairment, handicap, or disability. It will allow for more flexibility in the mode of working (from home or a company building or elsewhere) and representation (in person or virtual). Meetings like this workshop could easily take place within a 3-D virtual reality once the modes of interaction are available in real time and adaptable to different needs (see e.g., http://www.digitalspace.com/avatars/). Even private conversations during breaks could be easily arranged in this virtual reality. This virtual reality would be an alternative to travel. Multimodal input and output interfaces will allow human-computer (HC) interaction when sight is not available (e.g., for blind or sight-impaired users), when sight is an inappropriate medium (e.g., accessing computer information when driving a vehicle at high speeds), or when features and objects are occluded or distant.
2. NBIC has the potential to increase the quality of life of disabled people by allowing for alternative modes of transportation. One technique that could potentially increase quality of life immensely would be mobile teleportation devices. Teleportation would be linked to global positioning devices (see http://www.research.ibm.com/quantuminfo/teleportation/) so that someone could just teleport themselves where they have to go.

3. NBIC will allow for improving assistive devices for disabled people. For example, wheelchairs, which so far haven't changed much in the last 20 years, could be improved in several ways: nanomaterials could make them cheaper, lighter, and more durable; nanotechnology could be used to improve batteries or develop alternative energy generating devices (such as small fuel cells); NBIC could increase wheelchair capabilities (such as stair climbing) and make them more intelligent. The resulting device would allow a person sitting in it to move in any direction, horizontal or vertical, without regard to obstacles such as stairs. It have no need to physically attach to a surface for movement (it could hover). It would allow for the exploration of rough terrain such as the outdoors. This kind of personal moving/flying device could of course be developed for all people. NBIC also might lead to functional artificial limbs, which might even be better than existing human limbs. The same is true for the development of artificial devices for hearing, vision, and cognitive abilities such as comprehension and memory.
4. NBIC will greatly improve the functionality and design of houses, allowing voice command, intelligent applications, etc., that enable disabled (and elderly) people to be more independent.
5. NBIC has the potential to change the public space to make it much more user friendly and inclusive. Means will include IT advances to enable wearable

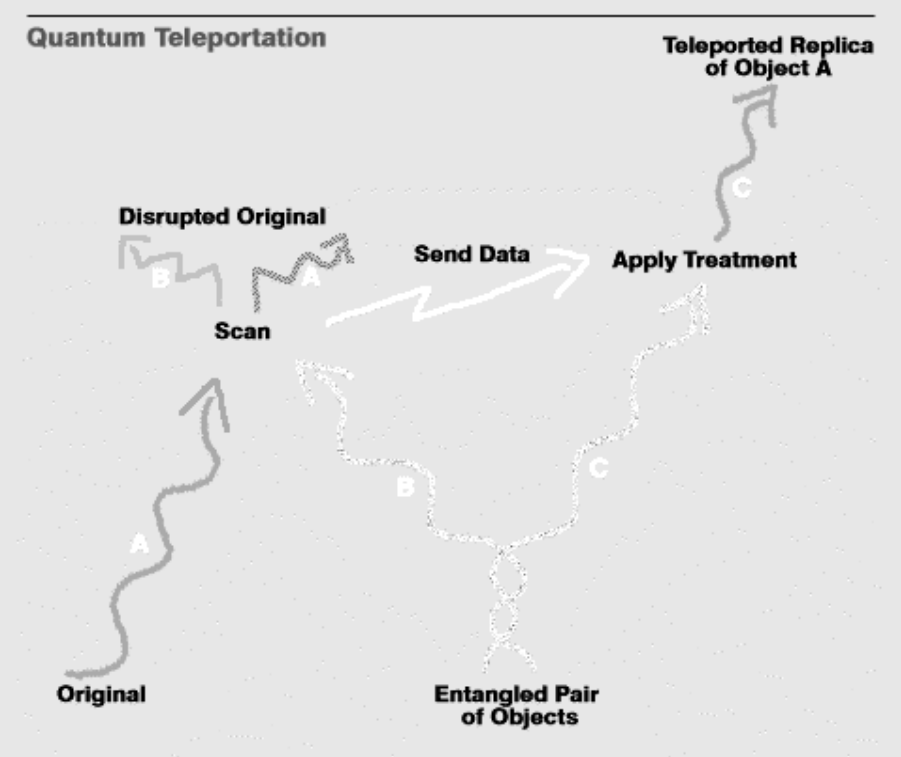

Figure C.18. On the quantum level this transport is achievable (Shahriar, Shapiro and Hemmer 2001). A mobile human teleportation device that can transport the person wherever the person wants to be would solve many accessibility and transportation problems.

computers for use in everyday living (e.g., finding when the next bus is due or where it is now); creation of smart environments (e.g., Remote Auditory Signage Systems [RASS] like talking signs, talking buses, etc., to facilitate wayfinding, business/object location identification, recognition of mass transit services, and intermodal transfer); use of IT and cognitive technology to develop voice-activated personal guidance systems using GPS and GIS; and multimodal interfaces to assist travel and environmental learning.

6. NBIC has the potential to improve communication on a global scale (e.g., universal translation devices), which would allow for a greater exchange of knowledge among people and a faster dissemination of advances in NBIC. The devices available today are not accurate and intelligent enough for use in day-to-day communication.
7. NBIC has the potential to help in the health management of disabled — and all — people.

The Role of Converging Technologies

The converging of technologies is needed if a systematic approach is to be undertaken to use technology for the benefit of disabled people. Often the same tool will have to rely on more than one technology to be workable (e.g., a wheelchair needs improved nanomaterials science for weight reduction and IT and cogno-science for new forms of control, leading to a whole new type of moving device such as a personal moving/flying device.)

The Transforming Strategy

The transforming strategy starts with the goal to increase the quality of life of disabled people. This goal makes it self-evident that disabled people have to be present at every brainstorming on every level, whether in government or private companies or in the public. These brainstorming activities will lead to the generation of ideas and identification of solutions for the goal. The generation of ideas and identifications leads to the identification of the technologies needed to implement these ideas and solutions. Technology is all the time used within a societal context; therefore, the societal dimension also has to be explored — leading to NBICs.

Estimated Implications

If the vision is fulfilled (and nothing indicates that the vision is not feasible), we should see a drop in unemployment of disabled people. A Canadian survey found the following three accommodations are most often identified by people with disabilities not in the labor force as being necessary for them to work: (1) modified/reduced hours (33%); (2) job redesign (27%); and (3) accessible transportation (14%). The above NBICs vision should help with the elimination of these three obstacles.

If the vision is fulfilled, we also should see an increase in the level of education and knowledge of disabled people (which in itself should translate into higher employment numbers). Higher levels of knowledge and employment would lead to higher income, and that would lead to better health. Thus, NBICs would lead to better integration of disabled people into society, making them more mobile and increasing their self-esteem. The disabled, including many elderly people, will feel

less isolated and will participate more in society, which will lead to many other effects, including increased well-being.

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D. ENHANCING GROUP AND SOCIETAL OUTCOMES

THEME D SUMMARY

Panel: J.S. Albus, W.S. Bainbridge, J. Banfield, M. Dastoor, C.A. Murray, K. Carley, M. Hirshbein, T. Masciangioli, T. Miller, R. Norwood, R. Price, P. Rubin, J. Sargent, G. Strong, W.A. Wallace

The third multidisciplinary theme is concerned with NBIC innovations whose benefits would chiefly be beyond the individual level, for groups, the economy, culture, or society as a whole. It naturally builds on the human cognition and physical capabilities themes and provides a background for the national security and scientific unification panels. In particular, it is focused on a nexus issue that relates logically to most technological applications discussed in this report and that connects all four NBIC scientific and technological realms — that is, how to enhance human communication and cooperation.

The starting point for enhancing group and societal outcomes was the workshop *Societal Implications of Nanoscience and Nanotechnology*, convened by the National Science Foundation September 28-29, 2000. Members of the 2001 workshop were all given copies of the earlier workshop report (Roco and Bainbridge 2001), and they considered how to build on the earlier nanotechnology foundation to develop a broader vision giving equal weight to biotechnology, information technology, and cognitive science, with a focus on enhancing human performance.

The report of the 2000 workshop stressed that the study of the societal implications of nanotechnology must be an integral part of the National Nanotechnology Initiative, and the same is true for future NBIC efforts. The term *societal implications* refers not merely to the impact of technology on society, but also to the myriad ways in which social groups, networks, markets, and institutions may shape development of the technology. Also, as the report recognized, "...sober, technically competent research on the interactions between nanotechnology and society will help mute speculative hype and dispel some of the unfounded fears that sometimes accompany dramatic advances in scientific understanding" (Roco and Bainbridge 2001, v). Similarly, involvement of the social and behavioral sciences in the convergence of NBIC disciplines will help maximize the gains that can be achieved in human performance.

Participants first considered a wide range of likely group and societal benefits of NBIC convergence, then developed the specific vision that they judge has the greatest potential and requires the most concentrated scientific effort to achieve.

There are many potential society-wide benefits of NBIC. Working together, the NBIC sciences and technologies can increase American productivity sufficiently to maintain U.S. world leadership, solve the Social Security shortfall, and eventually eliminate poverty in the nation. NBIC can significantly help us proactively deal with the environment, create new energy sources that will reduce our reliance on foreign oil, and ensure the sustainability of our economy. Multidisciplinary research could develop a secure national integrated data system for health data that relies on nano-

bio interfaces to obtain, update, and monitor personal data. Combined with new treatments and preventive measures based on NBIC convergence, such a system will extend life and improve its quality. NBIC industries of the future will employ distributed manufacturing, remote design, and production management for individualized products; cognitive control through simulated human intelligence; and a host of other techniques that will promote progress. In addition, converging technologies promise advances in simultaneous group interaction by using cognitive engineering and other new strategies.

In the vast array of very significant potential benefits of NBIC, one stands out that would catalyze all the others and that would require a special, focused effort to achieve success in the 10-20 year time frame. The panel strongly asserted that work should begin now to create *The Communicator*, a mobile system designed to enhance group communication and overcome barriers that currently prevent people from cooperating effectively. A concentrated effort involving nanotechnology, biotechnology, information technology, and cognitive science could develop in one or two decades a mature system to revolutionize people's capability to work together regardless of location or context.

The Communicator: Enhancing Group Communication, Efficiency, and Creativity

The Communicator is envisioned as a multifaceted system relying on the development of convergent technologies to enhance group communication in a wide variety of situations, including formal business or government meetings, informal social interaction, on the battlefield, and in the classroom. This system will rely on expected advances in nanotechnology fabrication and emerging information technologies, tightly coupled with knowledge obtained from the biological and cognitive domains. The convergence of these technologies will enhance individual attributes and remove barriers to group communication such as incompatible communication technologies, users' physical disabilities, language differences, geographic distance, and disparity in knowledge possessed by group members.

At the heart of The Communicator will be nano/info technologies that let individuals carry with them information about themselves and their work that can be easily shared in group situations. Thus, each individual participant will have the option to add information to the common pool of knowledge, across all domains of human experience — from practical facts about a joint task, to personal feelings about the issues faced by the group, to the goals that motivate the individual's participation.

The Communicator will also be a facilitator for group communication, an educator or trainer, and/or a translator, with the ability to tailor its personal appearance, presentation style, and activities to group and individual needs. It will be able to operate in a variety of modes, including instructor-to-group and peer-to-peer interaction, with adaptive avatars that are able to change their affective behavior to fit not only individuals and groups, but also varying situations. It will operate in multiple modalities, such as sight and sound, statistics and text, real and virtual circumstances, which can be selected and combined as needed in different ways by different participants. Improving group interactions via brain-to-brain and brain-machine-brain interactions will also be explored.

In total, a Communicator system with these attributes will be able to help overcome inequality between people, isolation of the individual from the environment, injustice and deprivation, personal and cultural biases, misunderstanding, and unnecessary conflict. In the broadest sense, it will be a powerful enhancer of communication and creativity, potentially of great economic and social benefit.

Statements and Visions

The collective vision, called The Communicator here, draws together numerous applications and sciences. In particular, it connects cognitive science and the individual-centered behavioral sciences to the broad range of group-centered social sciences. In addition, this chapter includes a vision for future transport aircraft. Thus, the statements and visions contributed by members of this working group naturally include social and well as behavioral science approaches and form a bridge back to the Roco and Bainbridge 2001 report on the societal implications of nanotechnology.

Reference

Roco, M.C. and W.S. Bainbridge, eds. 2001. *Societal Implications of Nanoscience and Nanotechnology*. Dordrecht, Netherlands: Kluwer.

STATEMENTS

COGNITION, SOCIAL INTERACTION, COMMUNICATION, AND CONVERGENT TECHNOLOGIES

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I am impressed with how my teenaged daughter and her friends marshal current technology for group communication. Most of their use of this technology, including AOL "Instant Messaging," email, cellphones, and transportation, is for social interaction.

The technological world 20 years from now will be a very different one. Prognostication is not my specialty and seems like a dangerous enterprise; however, I can talk about some things that we can do to help shape our future. Some of these are merely extensions of current technology and our current abilities, but the critical considerations I want to mention are well beyond our current capabilities. The unifying vision for these comments is the merging of cognition and communication.

Imagine a future without cellphones, laptops, PDAs, and other cumbersome devices. Going beyond the existing smart environments described by Reg Golledge and his colleagues (see Golledge essay in Chapter B and Loomis essay in Chapter C), we will soon be moving through a world in which we are continuously broadcasting, receiving, storing, synthesizing, and manipulating information. We

[1] The views expressed in this essay do not necessarily represent the views of the National Science Foundation.

will be embedded in dynamic, continually changing communicative clouds of data signals that communicate information about place, location, language, identity, persona, meaning, and intent. How will social and personal interaction be restructured in this new world? How can we use cognition to help us fly through these clouds effectively? I will leave the first question to experts like Sherry Turkle (see essay in Chapter B), who have thought long and hard about them, and will, instead, briefly mention where we need to go in the area of cognition.

The approaches that we will use for social and group communication in 20 years will rely on a variety of cognitive considerations. Here is a partial listing.

- **Intent.** *Neuro-nano* technology, such as *neural interfaces*, will enable us to provide the direct guidance of choice and selection of behaviors based on cognitive intent. This will allow for binary and graded choice directly under cognitive control.
- **Adaptation**. Communication and knowledge systems will learn and adapt, based upon an understanding of human behavior. Fundamental to this is a serious consideration of the adaptive landscapes that characterize this new communicative, social world and how they mesh with our cognitive capabilities.
- **Perception, analysis, and action**. Embedded and distributed systems and sensors will be enhanced by our fundamental understanding of human perceptual and analytic behavior and skills, including the following: auditory and visual scene analysis (Biederman 1995; Bregman 1994); the visual control of action (Loomis and Beall 1998; Turvey and Remez 1979; and Warren 1988); multimodality, including vision, audition, gesture, and haptic sensing and manipulation (Cassell et al. 2000; and Turvey 1996); spatial cognition (Golledge 1999); linguistic analysis, including statistically-based natural language processing and analysis (Biber, Conrad, and Reppen 1998; and Manning and Schutze 1999); and language use (Clark 1996).
- **Selection**. Cognitive selection, prioritization, and organization of information are essential if the information/communication clouds of the future are not to overwhelm us. Critical abilities to filter, organize, restrict, or enhance information will rely on cognitive selection, personal preference, and automatic adaptation that will evolve based on previous behavior, patterns, choices, and preferences.
- **Semantics**. Meaning will guide the performance of the systems of the future; it will be grounded by a variety of factors, including ties to the real world and its structure and requirements, biases, and personal and social needs. Semantically based systems will make communication more flexible, effective, and natural.
- **Self-organization and complexity.** Increasingly, approaches to understanding human cognition, perception, and behavior will rely on more sophisticated analytic, statistical, and conceptual tools. Examples include nonlinear dynamical systems; self-organization, complexity and emergent behavior; complex adaptive systems; agent-based modeling; naturalistic Bayesian-networks that include subjectively-based categorization and representation;

and the like (Holland 1995; Kauffman 1995, 2000; Kelso 1997; Varela et al. 1991; and Waldrop 1992. See also essay by J. Pollack in Chapter B).

What is needed to make these changes happen? First, they rely on the presumed convergence of nano-, bio-, info-, and cognitive technologies. Obviously, some of these changes are already on the way, particularly in the realm of nanotechnology, information technology, communication systems, and engineering. Progress has been significantly slower on the cognitive end, for a variety of reasons. The problems to be tackled in areas such as cognition and perception are often broad and very complex. These difficulties have been compounded by the need for noninvasive approaches for probing and exploring the human cognitive system. Mind and behavior have usually been explored from the outside. In essence, the cognitive system has been treated as a "black box" that can be probed in a variety of ways. Often such approaches have been conducted independently of the constraints imposed both by human physiology and by the environment. Other techniques that are more invasive, such as lesion studies, work with a system that is not in its normal functioning state. The difficulties in probing this system hamper our understanding of it.

Recent technological advances have raised the possibility of obtaining additional data about neural functioning during normal cognitive activities that can help to inform and constrain our theorizing. New advances in functional neuroimaging, including fMRI, PET, and MEG, coupled with the detailed study of neural circuitry and the theoretical advances in a number of areas, hold great promise (Gazzaniga et al. 1998; Lyon and Rumsey 1996; Marantz et al. 2000; and Posner and Raichle 1997). Functional imaging has the potential to be the telescope that lets us observe the universe of the mind. The goal is not to localize behavior but to have a tool that can potentially aid in understanding a massively complex system and in exploring brain behavior. However, these techniques will not be adequate on their own. They must be used in the context of a basic understanding of human cognition, perception, learning, development, and so forth.

Unfortunately, the fundamental understanding of how cognition works in areas such as spatial and cognition perception (auditory, haptic, and visual) has been massively underestimated. These are complex problems that will require significant basic research. For example, we need to understand our interaction with the world before we can fully understand the role the brain plays in helping us navigate this world. Before we can fully understand the role of the brain in vision, we must have a better depiction of what is available in the world for us to see. Before we fully understand the role of the brain in language, we need a clear theoretical understanding of what language is, how it is structured and organized at a variety of levels. Considerable progress that has been made in such areas points to the promise of theory-based research coupled with emerging technologies for visualization and simulation.

The "intelligent" systems of the future that will be fundamental to group and social communication will be far removed from the expert systems and the ungrounded formal systems of the artificial intelligence (AI) of past years. Instead, they will rely on the gains made in the fundamental understanding of the psychology, biology, and neuroscience of human behavior and performance, including cognition, perception, action, emotion, motivation, multimodality, spatial

and social cognition, adaptation, linguistic analysis, and semantics. These gains will be enhanced by consideration of human behavior as a complex adaptive biological system tightly coupled to its physical and social environment.

It remains to be seen whether the national support that is necessary to make substantial progress in these areas of cognition that hold such promise is forthcoming. However, if we hope to see truly convergent technologies leading to smart devices and the enhancement of human behavior, communication, and quality of life, we must tackle the difficult problems related to cognition on the large scale more commonly seen in areas such as computer science and engineering. Now is the time to seriously begin this effort.

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ENGINEERING THE SCIENCE OF COGNITION TO ENHANCE HUMAN PERFORMANCE

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The purpose of this paper is to provide a rationale for a new program whose purpose would be to integrate the science of cognition with technology to improve the performance of humans. We consider *cognition* to be "thinking" by individuals and, through consideration of emergent properties, "thinking" by groups, organizations, and societies. *Technology* is all the means employed by a social group to support its activities, in our case, to improve human performance. *Engineering* is the creation of artifacts such as technologies. Therefore, research concerned with engineering the science of cognition to improve human performance means research on the planning, design, construction, and implementation of technologies.

The purpose of such research should be to enhance performance, i.e., goal-directed behavior in a task environment, across all four levels of cognition: individual, group, organization, and society. In order to do so, we must consider the effective *integration* of cognition and technology as follows:

- integration of technology into the human central nervous system
- integration of important features of human cognition into machines
- integration of technologies (cognitive prosthetics) into the task environment to enhance human performance.

We see a synergistic combination of convergent technologies as starting with cognitive science (including cognitive neuroscience) since we need to understand the how, why, where, and when of thinking at all four levels in order to plan and design technology. Then we can employ nanoscience and nanotechnology to build the technology and biotechnology and biomedicine to implement it. Finally, we can employ information technology to monitor and control the technology, making it work.

ENGINEERING OF MIND TO ENHANCE HUMAN PRODUCTIVITY

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We have only just entered an era in history in which technology is making it possible to seriously address scientific questions regarding the nature of mind. Prior to about 125 years ago, inquiry into the nature of mind was confined to the realm of philosophy. During the first half of the 20th century, the study of mind expanded to include neuroanatomy, behavioral psychology, and psychoanalysis. The last 50 years have witnessed an explosion of knowledge in neuroscience and computational theory. The 1990s, in particular, produced an enormous expansion of understanding

of the molecular and cellular processes that enable computation in the neural substrate, and more is being learned, at a faster rate, than almost anyone can comprehend:

- Research on mental disease and drug therapy has led to a wealth of knowledge about the role of various chemical transmitters in the mechanisms of neurotransmission.
- Single-cell recordings of neural responses to different kinds of stimuli have shown much about how sensory information is processed and muscles are controlled.
- The technology of brain imaging is now making it possible to visually observe where and when specific computational functions are performed in the brain.
- Researchers can literally see patterns of neural activity that reveal how computational modules work together during the complex phenomena of sensory processing, world modeling, value judgment, and behavior generation.
- It has become possible to visualize what neuronal modules in the brain are active when people are thinking about specific things and to observe abnormalities that can be directly related to clinical symptoms (Carter 1998).

The Brain and Artificial Intelligence

In parallel developments, research in artificial intelligence and robotics has produced significant results in planning, problem-solving, rule-based reasoning, image analysis, and speech understanding. All of the fields below are active, and there exists an enormous and rapidly growing literature in each of the following areas:

- Research in learning automata, neural nets, fuzzy systems, and brain modeling is providing insights into adaptation and learning and knowledge of the similarities and differences between neuronal and electronic computing processes.
- Game theory and operations research have developed methods for decision-making in the face of uncertainty.
- Genetic algorithms and evolutionary programming have developed methods for getting computers to generate successful behavior without being explicitly programmed to do so.
- Autonomous vehicle research has produced advances in realtime sensory processing, world modeling, navigation, path planning, and obstacle avoidance.
- Intelligent vehicles and weapons systems are beginning to perform complex military tasks with precision and reliability.
- Research in industrial automation and process control has produced hierarchical control systems, distributed databases, and models for representing processes and products.
- Computer-integrated manufacturing research has achieved major advances in the representation of knowledge about object geometry, process planning,

network communications, and intelligent control for a wide variety of manufacturing operations.

- Modern control theory has developed precise understanding of stability, adaptability, and controllability under various conditions of uncertainty and noise.
- Research in sonar, radar, and optical signal processing has developed methods for fusing sensory input from multiple sources and for assessing the believability of noisy data.

In the field of *software engineering*, progress is also rapid, after many years of disappointing results. Much has been learned about how to write code for software agents and build complex systems that process signals, understand images, model the world, reason and plan, and control complex behavior. Despite many false starts and overly optimistic predictions, artificial intelligence, intelligent control, intelligent manufacturing systems, and smart weapons systems have begun to deliver solid accomplishments:

- We are learning how to build systems that learn from experience, as well as from teachers and programmers.
- We understand how to use computers to measure attributes of objects and events in space and time.
- We know how to extract information, recognize patterns, detect events, represent knowledge, and classify and evaluate objects, events, and situations.
- We know how to build internal representations of objects, events, and situations and how to produce computer-generated maps, images, movies, and virtual reality environments.
- We have algorithms that can evaluate cost and benefit, make plans, and control machines.
- We have engineering methods for extracting signals from noise.
- We have solid mathematical procedures for making decisions amid uncertainty.
- We are developing new manufacturing techniques to make sensors tiny, reliable, and cheap.
- Special-purpose integrated circuits can now be designed to implement neural networks or perform parallel operations such as are required for low-level image processing.
- We know how to build human-machine interfaces that enable close coupling between humans and machines.
- We are developing vehicles that can drive without human operators on roads and off.
- We are discovering how to build controllers that generate autonomous tactical behaviors under battlefield conditions.

As the fields of brain research and intelligent systems engineering converge, the probability grows that we may be able to construct what Edelman (1999) calls a

"conscious artifact." Such a development would provide answers to many long-standing scientific questions regarding the relationship between the mind and the body. At the very least, building artificial models of the mind would provide new insights into mental illness, depression, pain, and the physical bases of perception, cognition, and behavior. It would open up new lines of research into questions that hitherto have not been amenable to scientific investigation:

- We may be able to understand and describe intentions, beliefs, desires, feelings, and motives in terms of computational processes with the same degree of precision that we now can apply to the exchange of energy and mass in radioactive decay or to the sequencing of amino acid pairs in DNA.
- We may discover whether humans are unique among the animals in their ability to have feelings and start to answer the questions,
  - To what extent do humans alone have the ability to experience pain, pleasure, love, hate, jealousy, pride, and greed?
  - Is it possible for artificial minds to appreciate beauty and harmony or comprehend abstract concepts such as truth, justice, meaning, and fairness?
  - Can silicon-based intelligence exhibit kindness or show empathy?
  - Can machines pay attention, be surprised, or have a sense of humor?
  - Can machines feel reverence, worship God, be agnostic?

Engineering Intelligent Systems

The book *Engineering of Mind: An Introduction to the Science of Intelligent Systems* (Albus and Meystel 2001) outlines the main streams of research that we believe will eventually converge in a scientific theory that can support and bring about the engineering of mind. We believe that our research approach can enable the design of intelligent systems that pursue goals, imagine the future, make plans, and react to what they see, feel, hear, smell, and taste. We argue that highly intelligent behavior can be achieved by decomposing goals and plans through many hierarchical levels, with knowledge represented in a world model at the appropriate range and resolution at each level. We describe how a high degree of intelligence can be achieved using a rich dynamic world model that includes both *a priori* knowledge and information provided by sensors and a sensory processing system. We suggest how intelligent decision-making can be facilitated by a value judgment system that evaluates what is good and bad, important and trivial, and one that estimates cost, benefit, and risk of potential future actions. This will enable the development of systems that behave as if they are sentient, knowing, caring, creative individuals motivated by hope, fear, pain, pleasure, love, hate, curiosity, and a sense of priorities.

We believe that this line of research on highly intelligent systems will yield important insights into elements of mind such as attention, gestalt grouping, filtering, classification, imagination, thinking, communication, intention, motivation, and subjective experience. As the systems we build grow increasingly intelligent, we will begin to see the outlines of what can only be called mind. We hypothesize that mind is a phenomenon that will emerge when intelligent systems achieve a certain

level of sophistication in sensing, perception, cognition, reasoning, planning, and control of behavior.

There are good reasons to believe that the computing power to achieve human levels of intelligence will be achieved within a few decades. Since computers were invented about a half-century ago, the rate of progress in computer technology has been astounding. Since the early 1950s, computing power has doubled about every three years. This is a compound growth rate of a factor of ten per decade, a factor of 100 every two decades. This growth rate shows no sign of slowing and, in fact, is accelerating: during the 1990s, computing power doubled every 18 months — a factor of ten every five years. Today, a typical personal computer costing less than $1000 has more computing power than a top-of-the-line supercomputer of only two decades ago. One giga-op (one billion operations per second) single-board computers are now on the market. There appears to be no theoretical limit that will slow the rate of growth in computing power for at least the next few decades. This means that within 10 years, a relatively inexpensive network of 10 single-board computers could have computational power approaching one tera-ops (one trillion, or 10^{12} operations per second). Within 20 years, 10 single-board computers will be capable of 10^{14} operations per second. This is equivalent to the estimated computational power of the human brain (Moravec 1999). Thus, it seems quite likely that within two decades, the computing power will exist to build machines that are functionally equivalent to the human brain.

Of course, more than raw computing power is necessary to build machines that achieve human levels of performance. But the knowledge of how to utilize this computing power to generate highly intelligent behavior is developing faster than most people appreciate. Progress is rapid in many different fields. Recent results from a number of disciplines have established the foundations for a theoretical framework that might best be called a "computational theory of mind." In our book, Meystel and I have organized these results into a reference model architecture that we believe can be used to organize massive amounts of computational power into intelligent systems with human-level capabilities. This reference model architecture consists of a hierarchy of massively parallel computational modules and data structures interconnected by information pathways that enable analysis of the past, estimation of the present, and prediction of the future.

This architecture specifies a rich dynamic internal model of the world that can represent entities, events, relationships, images, and maps in support of higher levels of intelligent behavior. This model enables goals, motives, and priorities to be decomposed into behavioral trajectories that achieve or maintain goal states. Our reference architecture accommodates concepts from artificial intelligence, control theory, image understanding, signal processing, and decision theory. We demonstrate how algorithms, procedures, and data embedded within this architecture can enable the analysis of situations, the formulation of plans, the choice of behaviors, and the computation of current and expected rewards, punishments, costs, benefits, risks, priorities, and motives.

Our reference model architecture suggests an engineering methodology for the design and construction of intelligent machine systems. This architecture consists of layers of interconnected computational nodes, each containing elements of sensory processing, world modeling, value judgment, and behavior generation. At lower

levels, these elements generate goal-seeking reactive behavior; at higher levels, they enable perception, cognition, reasoning, imagination, and planning. Within each level, the product of range and resolution in time and space is limited: at low levels, range is short and resolution is high, whereas at high levels, range is long and resolution is low. This enables high precision and quick response to be achieved at low levels over short intervals of time and space, while long-range plans and abstract concepts can be formulated at high levels over broad regions of time and space.

Our reference model architecture is expressed in terms of the Realtime Control System (RCS) that has been developed at the National Institute of Standards and Technology and elsewhere over the last 25 years. RCS provides a design methodology, software development tools, and a library of software that is free and available via the Internet. Application experience with RCS provides examples of how this reference model can be applied to problems of practical importance. As a result of this experience, we believe that the engineering of mind is a feasible scientific goal that could be achieved within the next quarter century.

Implications for the Future

Clearly, the ability to build highly intelligent machine systems will have profound implications — in four important areas in particular: science, economic prosperity, military power, and human well-being, as detailed below.

Science

All of science revolves around three fundamental questions:

1. What is the nature of matter and energy?
2. What is the nature of life?
3. What is the nature of mind?

Over the past 300 years, research in the physical sciences has produced a wealth of knowledge about the nature of matter and energy, both on our own planet and in the distant galaxies. We have developed mathematical models that enable us to understand at a very deep level what matter is, what holds it together, and what gives it its properties. Our models of physics and chemistry can predict with incredible precision how matter and energy will interact under an enormous range of conditions. We have a deep understanding of what makes the physical universe behave as it does. Our knowledge includes precise mathematical models that stretch over time and space from the scale of quarks to the scale of galaxies.

Over the past half-century, the biological sciences have produced a revolution in knowledge about the nature of life. We have developed a wonderfully powerful model of the molecular mechanisms of life. The first draft of the human genome has been published. We may soon understand how to cure cancer and prevent AIDS. We are witnessing an explosion in the development of new drugs and new sources of food. Within the next century, biological sciences may eliminate hunger, eradicate most diseases, and discover how to slow or even reverse the aging process.

Yet, of the three fundamental questions of science, the most profound may be, “What is mind?” Certainly this is the question that is most relevant to understanding the fundamental nature of human beings. We share most of our body chemistry with all living mammals. Our DNA differs from that of chimpanzees by only a tiny

percentage of the words in the genetic code. Even the human brain is similar in many respects to the brains of apes. Who we are, what makes us unique, and what distinguishes us from the rest of creation lies not in our physical elements, or even in our biological makeup, but in our minds.

It is only the mind that sharply distinguishes the human race from all the other species. It is the mind that enables humans to understand and use language, to manufacture and use tools, to tell stories, to compute with numbers, and to reason with rules of logic. It is the mind that enables us to compose music and poetry, to worship, to develop technology, and to organize political and religious institutions. It is the mind that enabled humans to discover how to make fire, to build a wheel, to navigate a ship, to smelt copper, refine steel, split the atom, and travel to the moon.

The mind is a process that emerges from neuronal activity within the brain. The human brain is arguably the most complex structure in the known universe. Compared to the brain, the atom is an uncomplicated bundle of mass and energy that is easily studied and well understood. Compared to the brain, the genetic code embedded in the double helix of DNA is relatively straightforward. Compared to the brain, the molecular mechanisms that replicate and retrieve information stored in the genes are quite primitive. One of the greatest mysteries in science is how the computational mechanisms in the brain generate and coordinate the images, feelings, memories, urges, desires, conceits, loves, hatreds, beliefs, pleasures, disappointment, and pain that make up human experience. The really great scientific question is "What causes us to think, imagine, hope, fear, dream, and act like we do?" Understanding the nature of mind may be the most interesting and challenging problem in all of science.

Economic Prosperity

Intelligent machines can and do create wealth. And as they become more intelligent, they will create more wealth. Intelligent machines will have a profound impact on the production of goods and services. Until the invention of the computer, economic wealth (i.e., goods and services) could not be generated without a significant amount of human labor (Mankiw 1992). This places a fundamental limit on average per capita income. Average income cannot exceed average worker productive output. However, the introduction of the computer into the production process is enabling the creation of wealth with little or no human labor. This removes the limit to average per capita income. It will almost certainly produce a new industrial revolution (Toffler 1980).

The first industrial revolution was triggered by the invention of the steam engine and the discovery of electricity. It was based on the substitution of mechanical energy for muscle power in the production of goods and services. The first industrial revolution produced an explosion in the ability to produce material wealth. This led to the emergence of new economic and political institutions. A prosperous middle class based on industrial production and commerce replaced aristocracies based on slavery. In all the thousands of centuries prior to the first industrial revolution, the vast majority of humans existed near the threshold of survival, and every major civilization was based on slavery or serfdom. Yet, less than 300 years after the beginning of the first industrial revolution, slavery has almost disappeared, and a

large percentage of the world's population lives in a manner that far surpasses the wildest utopian fantasies of former generations.

There is good reason to believe that the next industrial revolution will change human history at least as profoundly as the first. The application of computers to the control of industrial processes is bringing into being a new generation of machines that can create wealth largely or completely unassisted by human beings. The next industrial revolution, sometimes referred to as the robot revolution, has been triggered by the invention of the computer. It is based on the substitution of electronic computation for the human brain in the control of machines and industrial processes. As intelligent machine systems become more and more skilled and numerous in the production process, productivity will rise and the cost of labor, capital, and material will spiral downward. This will have a profound impact on the structure of civilization. It will undoubtedly give rise to new social class structures and new political and economic institutions (Albus 1976).

The Role of Productivity

The fundamental importance of productivity on economic prosperity can be seen from the following equation:

Output = Productivity x Input

where

Input = labor + capital + raw materials

and

Productivity = the efficiency by which the input of labor, capital, and raw material is transformed into output product

Productivity is a function of knowledge and skill, i.e., technology. Growth in productivity depends on improved technology. The rapid growth in computer technology has produced an unexpectedly rapid increase in productivity that has confounded predictions of slow economic growth made by establishment economists only a decade ago (Symposia 1988; Bluestone and Harrison 2000). In the future, the introduction of truly intelligent machines could cause productivity to grow even faster. Given only conservative estimates of growth in computer power, unprecedented rates of productivity growth could become the norm as intelligent machines become pervasive in the productive process.

Intelligent systems have the potential to produce significant productivity improvements in many sectors of the economy, both in the short term and in the long term. Already, computer-controlled machines routinely perform economically valuable tasks in manufacturing, construction, transportation, business, communications, entertainment, education, waste management, hospital and nursing support, physical security, agriculture and food processing, mining and drilling, and undersea and planetary exploration.

As intelligent systems become widespread and inexpensive, productivity will grow and the rate of wealth production will increase. Intelligent machines in manufacturing and construction will increase the stock of wealth and reduce the cost of material goods and services. Intelligent systems in health care will improve services and reduce costs for the sick and elderly. Intelligent systems could make

quality education available to all. Intelligent systems will make it possible to clean up and recycle waste, reduce pollution, and create environmentally friendly methods of production and consumption.

The potential impact of intelligent machines is magnified by that fact that technology has reached the point where intelligent machines have begun to exhibit a capacity for self-reproduction. John von Neumann (1966) was among the first to recognize that machines can possess the ability to reproduce. Using mathematics of finite state machines and Turing machines, von Neumann developed a theoretical proof that machines can reproduce. Over the past two decades, the theoretical possibility of machine reproduction has been empirically demonstrated (at least in part) in the practical world of manufacturing:

- Computers are routinely involved in the processes of manufacturing computers
- Computers are indispensable to the process of designing, testing, manufacturing, programming, and servicing computers
- On a more global scale, intelligent factories build components for intelligent factories

At a high level of abstraction, many of the fundamental processes of biological and machine reproduction are similar. Some might object to a comparison between biological and machine reproduction on the grounds that the processes of manufacturing and engineering are fundamentally different from the processes of biological reproduction and evolution. Certainly there are many essential differences between biological and machine reproduction. But the comparison is not entirely far-fetched. And the results can be quite similar. Both biological and machine reproduction can produce populations that grow exponentially. In fact, machine reproduction can be much faster than biological. Intelligent machines can flow from a production line at a rate of many per hour.

Perhaps more important, machines can evolve from one generation to the next much faster and more efficiently than biological organisms. Biological organisms evolve by a Darwinian process, through random mutation and natural selection. Intelligent machines evolve by a Lamarckian process, through conscious design improvements under selective pressures of the marketplace. In the machine evolutionary process, one generation of computers often is used to design and manufacture the next generation of more powerful and less costly computers. Significant improvements can occur in a very short time between one generation of machines and the next. As a result, intelligent machines are evolving extremely quickly relative to biological species. Improved models of computer systems appear every few months to vie with each other in the marketplace. Those that survive and are profitable are improved and enhanced. Those that are economic failures are abandoned. Entire species of computers evolve and are superceded within a single decade. In other words, machine reproduction, like biological reproduction, is subject to evolutionary pressures that tend to reward success and punish failure.

The ability of intelligent systems to reproduce and evolve will have a profound effect on the capacity for wealth production. As intelligent machines reproduce, their numbers will multiply, leading to an exponential increase in the intelligent machine population. Since intelligent machines can increase productivity and

produce wealth, this implies that with each new generation of machine, goods, and services will become dramatically less expensive and more plentiful, while per capita wealth will increase exponentially.

The Prospects for Technology Growth

It is sometimes argued that technology, and therefore productivity, cannot grow forever because of the law of diminishing returns. It is argued that there must be a limit to everything, and therefore, productivity cannot grow indefinitely. Whether this is true in an abstract sense is an interesting philosophical question. Whether it is true in any practical sense is clear: it is not. From the beginning of human civilization until now, it remains a fact that the more that is known, the easier it is to discover new knowledge. And there is nothing to suggest that knowledge will be subject to the law of diminishing returns in the foreseeable future. Most of the scientists who have ever lived are alive and working today. Scientists and engineers today are better educated and have better tools with which to work than ever before. In the neurological and cognitive sciences, the pace of discovery is astonishing. The same is true in computer science, electronics, manufacturing, and many other fields. Today, there is an explosion of new knowledge in almost every field of science and technology.

There is certainly no evidence that we are nearing a unique point in history where progress will be limited by an upper bound on what there is to know. There is no reason to believe that such a limit even exists, much less that we are approaching it. On the contrary, there is good evidence that the advent of intelligent machines has placed us on the cusp of a growth curve where productivity can grow exponentially for many decades, if not indefinitely. Productivity growth is directly related to growth in knowledge. Growth in knowledge is dependent on the amount and effectiveness of investment in research, development, and education. This suggests that, given adequate investment in technology, productivity growth could return to 2.5 percent per year, which is the average for the 20th century. With higher rates of investment, productivity growth could conceivably rise to 4 percent, which is the average for the 1960-68 time frame. Conceivably, with sufficient investment, productivity growth could exceed 10 percent, which occurred during the period between 1939 and 1945 (Samuelson and Nordhaus 1989).

If such productivity growth were to occur, society could afford to improve education, clean up the environment, and adopt less wasteful forms of production and consumption. Many social problems that result from slow economic growth, such as poverty, disease, and pollution, would virtually disappear. At the same time, taxes could be reduced, Social Security benefits increased, and healthcare and a minimum income could be provided for all. The productive capacity of intelligent machines could generate sufficient per capita wealth to support an aging population without raising payroll taxes on a shrinking human labor force. Over the next three decades, intelligent machines might provide the ultimate solution to the Social Security and Medicare crisis. Benefits and services for an aging population could be continuously expanded, even in countries with stable or declining populations.

Military Power

Intelligent systems technologies have the potential to revolutionize the art of war. The eventual impact on military science may be as great as the invention of

gunpowder, the airplane, or nuclear weapons. Intelligent weapons systems are already beginning to emerge. Cruise missiles, smart bombs, and unmanned reconnaissance aircraft have been deployed and used in combat with positive effect. Unmanned ground vehicles and computer-augmented command and control systems are currently being developed and will soon be deployed. Unmanned undersea vehicles are patrolling the oceans collecting data and gathering intelligence. These are but the vanguard of a whole new generation of military systems that will become possible as soon as intelligent systems engineering becomes a mature discipline (Gourley 2000).

In future wars, unmanned air vehicles, ground vehicles, ships, and undersea vehicles will be able to outperform manned systems. Many military systems are limited in performance because of the inability of the human body to tolerate high levels of temperature, acceleration, vibration, or pressure, or because humans need to consume air, water, and food. A great deal of the weight and power of current military vehicles is spent on armor and life support systems that would be unnecessary if there were no human operators on board. A great deal of military tactics and strategy is based on the need to minimize casualties and rescue people from danger. This would become unnecessary if warriors could remain out of harm's way.

Intelligent military systems will significantly reduce the cost of training and readiness. Compared to humans, unmanned vehicles and weapons systems will require little training or maintenance to maintain readiness. Unmanned systems can be stored in forward bases or at sea for long periods of time at low cost. They can be mobilized quickly in an emergency, and they will operate without fear under fire, the first time and every time.

Intelligent systems also enable fast and effective gathering, processing, and displaying of battlefield information. They can enable human commanders to be quicker and more thorough in planning operations and in replanning as unexpected events occur during the course of battle. In short, intelligent systems promise to multiply the capabilities of the armed forces, while reducing casualties and hostages and lowering the cost of training and readiness (Maggart and Markunas 2000).

Human Well-being

It seems clear that intelligent systems technology will have a profound impact on economic growth. In the long run, the development of intelligent machines could lead to a golden age of prosperity, not only in the industrialized nations, but throughout the world. Despite the explosion of material wealth produced by the first industrial revolution, poverty persists and remains a major problem throughout the world today. Poverty causes hunger and disease. It breeds ignorance, alienation, crime, and pollution. Poverty brings misery, pain, and suffering. It leads to substance abuse. Particularly in the third world, poverty may be the biggest single problem that exists, because it causes so many other problems. And yet there is a well-known cure for poverty. It is wealth.

Wealth is difficult to generate. Producing wealth requires labor, capital, and raw materials — multiplied by productivity. The amount of wealth that can be produced for a given amount of labor, capital, and raw materials depends on productivity. The level of productivity that exists today is determined by the current level of

knowledge embedded in workers' skills, management techniques, tools, equipment, and software used in the manufacturing process. In the future, the level of productivity will depend more and more on the level of knowledge embedded in intelligent machines. As the cost of computing power drops and the skills of intelligent machines grow, the capability for wealth production will grow exponentially. The central question then becomes, how will this wealth be distributed?

In the future, new economic theories based on abundance may emerge to replace current theories based on scarcity. New economic institutions and policies may arise to exploit the wealth-producing potential of large numbers of intelligent machines. As more wealth is produced without direct human labor, the distribution of income may shift from wages and salaries to dividends, interest, and rent. As more is invested in ownership of the means of production, more people may derive a substantial income from ownership of capital stock. Eventually, some form of people's capitalism may replace the current amalgam of capitalism and socialism that is prevalent in the industrialized world today (Albus 1976; Kelso and Hetter 1967).

Summary and Conclusions

We are at a point in history where science has good answers to questions such as, "What is the universe made of?" and "What are the fundamental mechanisms of life?" There exists a wealth of knowledge about how our bodies work. There are solid theories for how life began and how species evolved. However, we are just beginning to acquire a deep understanding of how the brain works and what the mind is.

We know a great deal about how the brain is wired and how neurons compute various functions. We have a good basic understanding of mathematics and computational theory. We understand how to build sensors, process sensory information, extract information from images, and detect entities and events. We understand the basic principles of attention, clustering, classification, and statistical analysis. We understand how to make decisions in the face of uncertainty. We know how to use knowledge about the world to predict the future, to reason, imagine, and plan actions to achieve goals. We have algorithms that can decide what is desirable and plan how to get it. We have procedures to estimate costs, risks, and benefits of potential actions. We can write computer programs to deal with uncertainty and compensate for unexpected events. We can build machines that can parse sentences and extract meaning from messages, at least within the constrained universe of formal languages.

As computing power increases and knowledge grows of how the brain converts computational power into intelligent behavior, the ability of machines to produce greater wealth (i.e., goods and services that people want and need) will enable many possible futures that could never before have been contemplated. Even under very conservative assumptions, the possibilities that can be generated from simple extrapolations of current trends are very exciting. We are at a point in history where some of the deepest mysteries are being revealed. We are discovering how the brain processes information, how it represents knowledge, how it makes decisions and controls actions. We are beginning to understand what the mind is. We will soon

have at our disposal the computational power to emulate many of the functional operations in the brain that give rise to the phenomena of intelligence and consciousness. We are learning how to organize what we know into an architecture and methodology for designing and building truly intelligent machines. And we are developing the capacity to experimentally test our theories. As a result, we are at the dawning of an age where the engineering of mind is feasible.

In our book (Albus and Meystel 2001), we have suggested one approach to the engineering of mind that we believe is promising, containing the following elements:

- *a perception system* that can fuse *a priori* knowledge with current experience and can understand what is happening, both in the outside world and inside the system itself
- *a world-modeling system* that can compute what to expect and predict what is likely to result from contemplated actions
- *a behavior-generating system* that can choose what it intends to do from a wide variety of options and can focus available resources on achieving its goals
- *a value judgment system* that can distinguish good from bad and decide what is desirable

We have outlined a reference model architecture for organizing the above functions into a truly intelligent system, hypothesizing that in the near future it will become possible to engineer intelligent machines with intentions and motives that use reason and logic to devise plans to accomplish their objectives.

Engineering of mind is an enterprise that will prove at least as technically challenging as the Apollo program or the Human Genome project. And we are convinced that the potential benefits for humankind will be at least as great, perhaps much greater. Understanding the mind and brain will bring major scientific advances in psychology, neuroscience, and education. A computational theory of mind may enable us to develop new tools to cure or control the effects of mental illness. It will certainly provide us with a much deeper appreciation of who we are and what our place is in the universe.

Understanding the mind and brain will enable the creation of a new species of intelligent machine systems that can generate economic wealth on a scale hitherto unimaginable. Within a half-century, intelligent machines might create the wealth needed to provide food, clothing, shelter, education, medical care, a clean environment, and physical and financial security for the entire world population. Intelligent machines may eventually generate the production capacity to support universal prosperity and financial security for all human beings. Thus, the engineering of mind is much more than the pursuit of scientific curiosity. It is more even than a monumental technological challenge. It is an opportunity to eradicate poverty and usher in a golden age for all humankind.

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MAKING SENSE OF THE WORLD: CONVERGENT TECHNOLOGIES FOR ENVIRONMENTAL SCIENCE

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Through the combination of geoscience, biology, and nano- and information technologies, we can develop a fundamental understanding of the factors that define and regulate Earth's environments from the molecular to global scale. It is essential that we capture the complex, interconnected nature of the processes that maintain the habitability of the planet in order to appropriately utilize Earth's resources and predict, monitor, and manage global change. This goal requires long-term investments in nanogeoscience, nanotechnology, and biogeochemical systems modeling.

Introduction

Looking to the future, what are the greatest challenges our society (and the world) faces? Ensuring an adequate food supply, clean air, and clean water are problems intimately linked to the environment. Given the rate of accumulation of environmental damage, it seems appropriate to ask, can science and technology solve the problems associated with pollution and global change before it is too late? Where should we invest our scientific and technological efforts, and what might these investments yield?

One of the mysteries concerning environmental processes is the role of extremely small particles that, to date, have defied detection and/or characterization. We now realize that materials with dimensions on the nanometer scale (intermediate between

clusters and macroscopic crystals) are abundant and persistent in natural systems. Nanoparticles are products of, and substrates for, nucleation and growth in clouds. They are also the initial solids formed in water, soils, and sediments. They are generated in chemical weathering and biologically mediated redox reactions, during combustion of fuel, and in manufacturing. For example, nanoparticles are by-products of microbial energy generation reactions that utilize inorganic ions (e.g., Mn, Fe, S, U) as electron donors or acceptors. They are highly reactive due to their large surface areas, novel surface structures, and size-dependent ion adsorption characteristics and electronic structures (including redox potentials). It is likely that they exert a disproportionately large, but as yet incompletely defined, influence on environmental geochemistry because they provide a means for transport of insoluble ions and present abundant novel, reactive surfaces upon which reactions, including catalytic reactions, occur.

It is widely accepted that the most rapid growth in knowledge in recent years has occurred in the field of biology. In the environmental context, the biology of single-celled organisms represents a critically important focus, for several reasons. First, microbes are extraordinarily abundant. They underpin many of the biogeochemical cycles in the environment and thus directly impact the bioavailability of contaminants and nutrients in ecosystems. They are responsible for the formation of reactive mineral particles and contribute to mineral dissolution. With analysis of these connections comes the ability to use microbes to solve environmental problems. Second, microorganisms are relatively simple, hence detailed analysis of how they work represents a tractable problem. Third, microbes have invented ways to carry out chemical transformations via enzymatic pathways at low temperatures. These pathways have enormous industrial potential because they provide energetically inexpensive routes to extract, concentrate, and assemble materials needed by society. Identification of the relevant microbial enzymatic or biosynthetic pathways requires analysis of the full diversity of microbial life, with emphasis on organisms in extreme natural geologic settings where metabolisms are tested at their limits.

Where does our understanding of microbes and nanoparticles in the environment stand today? Despite the fact that microbes dominate every habitable environment on Earth, we know relatively little about how most microbial cells function. Similarly, we have only just begun to connect the novel properties and reactivity of nanoparticles documented in the laboratory to phenomena in the environment. Although our understanding of these topics is in its infancy, science is changing quickly. The center of this revolution is the combination of molecular biology, nanoscience, and geoscience.

The Role of Converging Technologies

In order to comprehensively understand how environmental systems operate at all scales, convergence of biological, technological, and geoscientific approaches is essential. Three important tasks are described below.

Identification and Analysis of Reactive Components in Complex Natural Systems

Nanoparticles and microorganisms are among the most abundant, most reactive components in natural systems. Natural nanoparticles (often < 5 nm in diameter) exhibit the same novel size-dependent properties that make their synthetic

equivalents technologically useful. The functions of some microbial cell components (e.g., cell membranes, ribosomes) probably also depend on size-related reactivity. A challenge for the immediate future is determination of the origin, diversity, and roles of nanoparticles in the environment. Similarly, it is critical that we move from detecting the full diversity of microorganisms in most natural systems to understanding their ranges of metabolic capabilities and the ways in which they shape their environments. These tasks require integrated characterization studies that provide molecular-level (inorganic and biochemical) resolution.

Massive numbers of genetic measurements are needed in order to identify and determine the activity of thousands of organisms in air, water, soils, and sediments. Enormous numbers of chemical measurements are also required in order to characterize the physical environment and to evaluate how biological and geochemical processes are interconnected. This task demands laboratory and field data that is spatially resolved at the submicron-scale at which heterogeneities are important, especially in interfacial regions where reactions are fastest. The use of robots in oceanographic monitoring studies is now standard, but this is only the beginning. Microscopic devices are needed to make *in situ*, fine-scale measurements of all parameters and to conduct *in situ* experiments (e.g., to assay microbial population makeup in algal blooms in the ocean or to determine which specific organism is responsible for biodegradation of an organic pollutant in a contaminated aquifer). These devices are also required for instrumentation of field sites to permit monitoring over hundreds of meters to kilometer-scale distances. Development of appropriate microsensors for these applications is essential.

Environmental science stands to benefit greatly from nanotechnology, especially if new sensors are developed with environmental monitoring needs in mind. In the most optimistic extreme, the sensors may be sufficiently small to penetrate the deep subsurface via submicron-scale pores and be able to relay their findings to data collection sites. It is likely that these extremely small, durable devices also will be useful for extraterrestrial exploration (e.g., Mars exploration).

Monitoring Processes in the Deep Subsurface

Many of the inorganic and organic contaminants and nutrients of interest in the environment may be sequestered at considerable depths in aquifers or geological repositories. Methods are needed to image the structure of the subsurface to locate and identify these compounds, determine the nature of their surroundings, and monitor changes occurring during natural or enhanced *in situ* remediation. Examples of problems for study include detection of nanoparticulate metal sulfide or uranium oxide minerals produced by biological reduction, possibly via geophysical methods; analysis of the role of transport of nanoparticulate contaminants away from underground nuclear waste repositories; and monitoring of the detailed pathways for groundwater flow and colloid transport.

Development of Models to Assist in Analysis of Complex, Interdependent Phenomena

After we have identified and determined the distributions of the reactive inorganic and organic nanoscale materials in natural systems, it is essential that we understand how interactions between these components shape the environment. For example, we anticipate development and validation of comprehensive new models

that integrate predictions of particle-particle organic aggregation and crystal growth with models that describe how aggregates are transported through porous materials in the subsurface. These developments are essential for prediction of the transport and fate of contaminants during and after environmental remediation.

Environmental processes operate across very large scales on continents and in the oceans. Thus, remote collection of high-resolution data sets (e.g., by satellite-based remote sensing) can also be anticipated. The large quantities of data from direct and indirect monitoring programs will benefit from new methodologies for information management. Mathematical models are essential to guide cognition and to communicate the principles that emerge from the analyses. An example of an ecosystem model is shown in Figure D.1. Input from the cognitive sciences will be invaluable to guide development of supermodels of complex processes.

The Transforming Strategy

The first task toward an integrated understanding of the Earth's ecosystems is to identify and study the most important components. Focus on microorganisms is warranted based on their sheer abundance and metabolic versatility. The first two disciplinary partners, molecular biology and nanoscience, have already taken center stage with the integration of molecular biology and genome-enabled technologies

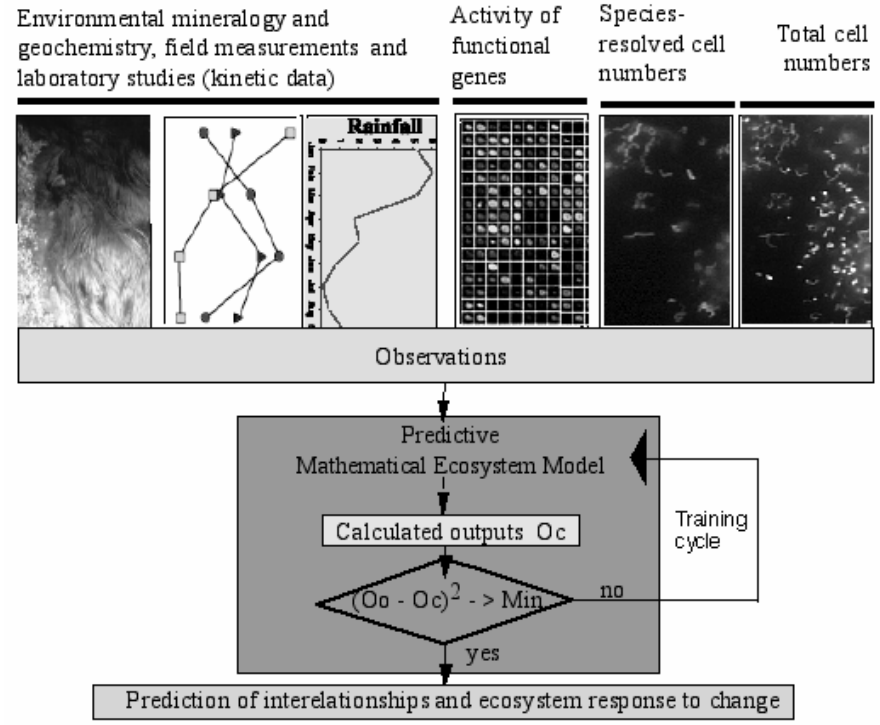

Figure D.1. Example of an ecosystem model that incorporates information about the physical and chemical environment with information about population size and structure and gene expression to analyze community interactions and predict response of the system to perturbations.

(e.g., whole genome expression microarrays). In the next few years, these tools will allow us to decipher the full diversity of ways in which individual organisms grow, develop, reproduce, and evolve. These breakthroughs are critical to medicine, agriculture, and biologically assisted manufacturing and waste management.

Inorganic components also play key roles in natural systems. As noted above, exceedingly small particles intermediate in size between molecular clusters and macroscopic materials (nanoparticles) are abundant components of natural environments. Study of nanoparticle formation, properties, and stability is at the intersection of nanoscience, biology, chemistry, and geoscience. The unique characteristics of materials structured on the nanoscale have long been appreciated in the fields of materials science and engineering. It is now essential that we determine whether the nanoparticles in soils, sediments, water, the atmosphere, and space also have unusual and environmentally important surface properties and reactivity. Do nanoparticles partition in natural systems in size-dependent ways? Are they transported readily in groundwater, and is this the mechanism by which insoluble contaminants and nutrients are dispersed? There are also potentially intriguing questions relating to interactions between inorganic nanoparticles and organic molecules. For example, do nanoparticles in dust react in unusual ways with organic molecules (perhaps in sunlight)? Is the assembly of nanoparticles by organic polymers central to biomineralization processes, such as generation of bone? Can these interactions be harnessed for biomimetic technologies? Did reactions at nanoparticle surfaces play a role in prebiotic synthesis or the origin of life? Were nanoparticles themselves captured by organic molecules to form early enzymes? The answers to these questions are important to our understanding of inorganic and biological systems. However, far larger challenges remain.

The second task will be to investigate entire communities of microorganisms at the genetic level to provide new insights into community structure and organization, including cell-cell signaling and the partitioning of function. This challenge requires complete genetic analysis of all community members without cultivation. This task will require extension of current biological, computational, and information technologies to permit simultaneous reconstruction of genome content from multiorganism assemblages at the level of strains without isolation of each community member. Resulting data will also allow comparison of the microbial community lifestyle — characterized by the ability to directly control the geochemical cycles of virtually every element — to its alternative, multicellular life. These analyses will also unveil the pathways by which all biologically and geochemically important transformations are accomplished. This work must be initiated in the laboratory, but ultimately, must be expanded to explicitly include all environmental parameters and stimuli. Consequently, the task of understanding organisms in their environments stands before us as the third and longest-term task.

An additional component, geoscience, must be included in order to meet the challenge of molecularly resolved ecology. Environmental applications have lagged behind investigations of organisms in the laboratory because natural systems are extremely complicated. Critical environmental data include time-resolved measurements of the structure and organization of natural systems, organism population statistics, measurements of the levels of expression of all genes within communities of interacting species, and quantification of how these expression

patterns are controlled by and control geochemical processes. This approach, which must ultimately include macroorganisms, will be essential for medical and agricultural, as well as environmental, reasons.

Education and Outreach

Analysis of complex systems, through integration of nanotechnology, nanoscience, geoscience, biology, ecology, and mathematics, will place special demands on the educational system. It will require training of a new generation of researchers with special experimental, communication, and quantitative reasoning skills. Because the task of ecosystem analysis is too large to be tackled in an individual project, it may be necessary to reconsider the structure of graduate student training programs. It is possible that traditional, carefully delineated, individual Ph.D. projects will be replaced by carefully integrated, collaborative Ph.D. research efforts that include individuals at all career levels. Changes such as this will have the added advantage of generating scientists that are able to work together to solve large, complicated problems.

The integration of science and technology to develop understanding of the environment should extend to all educational levels. For example, an effective use of nanotechnology may be to monitor processes in the vicinity of K-12 classrooms (e.g., bird migrations, air quality, pesticide degradation in soil) and to compare these data to those collected elsewhere. This may improve the public's appreciation of the Earth's environments as complex biogeochemical systems that change in definable and predictable ways as the result of human activities.

Conclusions

Molecularly resolved analyses of environmental systems will allow us to determine how increasingly complex systems, from the level of cells and microbial communities up to entire ecosystems at the planetary scale, respond to environmental perturbations. With this knowledge in hand, we can move toward rigorous determination of environmental state and prediction of ecosystem change.

High-resolution molecular- and nanometer-scale information from both inorganic and biological components of natural systems will dramatically enhance our ability to utilize microbial processes (such as light-harvesting molecules for solar cells or mineral-solubilizing enzymes for materials processing) for technological purposes. This may be of great importance if we are to reduce our dependence on energetically expensive manufacturing and existing energy resources. For example, bioleaching is an alternative to smelting, bioextraction is an alternative to electrochemistry, biosynthesis of polymers is an alternative to petroleum processing, biomineralization is an alternative to machine-based manufacturing. Ultimately, nano-bio-geo integration will allow us to tease apart the complex interdependencies between organisms and their surroundings so that we may ultimately gain sufficient understanding of environmental systems to avoid the fate of microorganisms grown in a petri dish (Figure D.2).

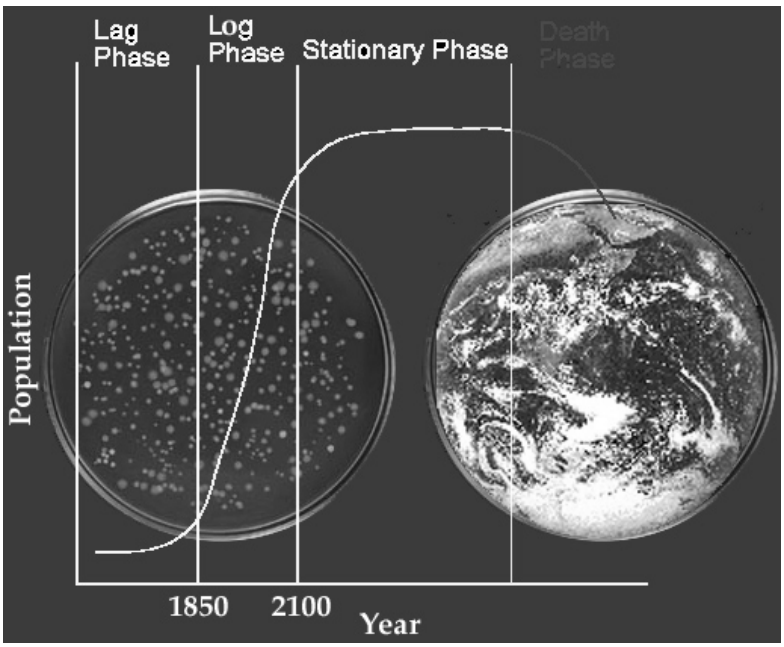

Figure D.2. Microbial communities growing within a confined space (here shown in a petri dish, left) have a cautionary tale to tell: overuse and/or unbalanced use of resources leads to build up of toxins, shortage of food, overpopulation, and death.

FUNDAMENTALLY NEW MANUFACTURING PROCESSES AND PRODUCTS

M.C. Roco, National Science Foundation, Chair, National Science and Technology Council's Subcommittee on Nanoscale Science, Engineering, and Technology (NSET)

Integration of NBIC tools is expected to lead to entirely new categories of materials, devices, and systems for use in manufacturing, construction, transportation, medicine, emerging technologies and scientific research. Nanotechnology, biotechnology and information technology will play an essential role in their research, design and production. Fundamental research will be at the confluence of physics, chemistry, biology, mathematics and engineering. Industries increasingly will use biological processes in manufacturing. Knowledge about the molecular level processes describing the growth and metabolism of living cells may be applied, through analogy, to development of inorganic materials. New products may include pharmaceutical genomics, electronic devices with three-dimensional architectures, large databases, software for realistic mutiphenomena/ multiscale simulation of systems from basic principles; and quantitative studies in social sciences. Cognitive sciences will provide better ways to design and use the new manufacturing processes, products and services.

Several paradigm changes are expected in each of the four NBIC domains:

- Nanotechnology is expected to move from its current focus on scientific discovery towards technological innovation, leading to systematic manufacturing methods for mass production
- Biotechnology will move towards molecular medicine and pharmaceutical genomics, and biosystems will be integrated on an increased rate in advanced materials and systems
- In information technology, the quest for smallness and speed will be enhanced by the focus for new architectures, three-dimensional design, functionality and integration with application driven developments in areas such as biosystems and knowledge based technologies;
- Cognitive sciences will focus explanation of human behavior from understanding of physico-chemical-biological processes at the nanoscale.

Broader range of research and development issues will need to be addressed. For example, one should consider the following issues in nanoscale engineering:

- Three dimensional material/device/system spatial/temporal architectures
- Directed assembling/patterning/tem plating for heterogeneous nanosystems
- Hybrid and bio nanosystems for medicine and manufacturing
- Energy conversion and transfer
- Mutiphenomena, multiprocessors, multiscale design, including large scale atomistic modeling and simulation
- Integration of nanoscale into larger scales: creation and use of intermediary standard components
- Thermal and chemical stability
- Operational and environmental safety
- Reliability and reproductibity at the nanoscale

New groups of fundamentally new technologies and products will develop. Examples are pharmaceutical genomics, biochips with complex functions, realistic simulation of phenomena and processes from the nanoscale, and new flight vehicles.

A new infrastructure based on four NBIC R&D platforms will be necessary, to be available anywhere, in short time and to any industry and all those interested.

Adopting new indices such as a modified GNP to include human dimension, impact on the environment, preparation of the infrastructure (including education) and other societal implications will be necessary in order to measure and calibrate the outcomes. New criteria, such as reducing the entropy of a system (for example: less energy dissipation per computation and transmission of information; less material, energy, water, pollution in nanotechnology; and less change/degradation in biotechnology).

Already NSF, NASA, EPA, DOD, DOE have several seed projects in developing R&D strategy based on unifying science and technology integration, creating infrastructure for research at the confluence of two or more NBIC domains, developing neuromorphic engineering, improving human performance, advancing

changes in education including "learning how to learn", and preparing for societal implications of converging technologies.

VISIONARY PROJECTS

THE COMMUNICATOR: ENHANCEMENT OF GROUP COMMUNICATION, EFFICIENCY, AND CREATIVITY

Philip Rubin, Murray Hirschbein, Tina Masciangioli, Tom Miller, Cherry Murray, R.L. Norwood, and John Sargent

As envisioned, *The Communicator* will be a "smart," multifaceted, technical support system that relies on the development of convergent technologies to help enhance human group communication in a wide variety of situations, including meetings (both formal and informal), social exchanges, workplace collaborations, real-world corporate or battle training situations, and educational settings. This system will rely on expected advances in nanotechnology, fabrication, and a number of emerging information technologies, both software and hardware. In this system, these technologies will be tightly coupled with knowledge obtained from the biological and cognitive domains. The convergence of these technologies will serve to enhance existing attributes of individuals and remove barriers to group communication. This system will consist of a set of expanding implementations of these convergent technologies, growing more complex as the individual technologies mature over time. Some of these implementations are described below.

The initial goal of The Communicator is simple: to remove the kinds of barriers that are presently common at meetings where participants rely for communication on similar but slightly varying technologies. For example, it is standard for meeting participants to use software such as *PowerPoint* to present their ideas, but they often encounter technical difficulties moving between computers and computer platforms different from those on which they created their presentations. The transfer of information between systems during meetings is often hampered by varying media, connector differences, and incompatible data standards. At its simplest level, The Communicator would serve as an equalizer for communication in such situations, detecting the technological requirements of each participant and automatically resolving any differences in the presentation systems. The transfer and presentation of information would then become transparent.

Moving beyond this initial implementation, The Communicator would serve to remove more significant communication barriers, such as those related to physical disabilities or language differences. For example, the system, once apprised of a group member's hearing impairment, could tailor a presentation to that participant's needs by captioning the spoken or other auditory information. Similarly, it could produce auditory transcriptions of information presented visually in a group situation for any visually impaired member of the group. It could also provide simultaneous translation of meeting proceedings into a number of languages.

At the heart of The Communicator system are nano/info technologies that will allow individuals to carry with them electronically stored information about themselves that they can easily broadcast as needed in group situations. Such information might include details about preferences, interests, and background. Early implementations of this approach are do-able now.

An even more interesting and advanced implementation would consist of detection and broadcast of the physiological and affective states of group participants with the purpose of providing resources to individuals and tailoring interactivity in order to allow the group to more easily achieve its goals. Detection of participants' physiological and affective states would be determined by monitoring biological information (such as galvanic skin response and heart rate) and cognitive factors via pattern recognition (such as face recognition to detect facial emotion, and voice pitch analysis to detect stress levels). Based on determinations of the needs and physical and cognitive states of participants, The Communicator could tailor the information it supplies to each individual, providing unique resources and improving productivity. Participants would have the ability to define or restrict the kinds of information about themselves that they would be willing to share with other members of the group.

As an example of this implementation, in an international conference or tribunal, each participant could select simultaneous translation of the discourse. Through PDA-like devices or biopatches, the system could measure the empathy levels or stress levels of all negotiators. A personal avatar would serve as a "coach" for each individual, recalling past statements, retrieving personal histories, and functioning as a research assistant to prepare material for use in arguments and deliberations. The system would facilitate the building of consensus by identifying areas of nominal disagreement and searching for common values and ideas.

Beyond facilitation of group communication, The Communicator could also serve as an educator or trainer, able to tailor its presentation and to operate in a variety of modes, including peer-to-peer interaction and instructor/facilitator interaction with a group. The Communicator would function as an adaptive avatar, able to change its personal appearance, persona, and affective behavior to fit not only individuals or groups but also varying situations.

Design Components

Several important distinct components of The Communicator, introduced below, should be carefully designed to work together seamlessly.

The Individual Information Component

One key element of The Communicator system will be a model or record of each individual, including how each individual interacts with the environment and how s/he prefers to do so. This would include information like the language spoken, the preferred sensory channel, and limitations on input and output. This system should also include characteristics of the individual's cognitive capabilities: learning speed, preferences for learning modalities, areas of expertise, leisure activities, history of important social events, and other attributes that are relevant to a given task or situation. Ways that this element could be applied include the following:

- Using bioauthentication, the system could identify each individual in a group, including specific kinds of information about each individual. This could shorten the initial socialization process in a group setting.
- Users would be able to specify that they receive input translated into specific languages, including captioning or signing if needed.
- The system could determine what stress levels, information density, and learning rates work best for the individuals and the group as a whole.
- The system could provide support so that the individual learns in whatever modality works best for the topic at hand: auditory, haptic, text, images, virtual reality, and any specialized modality with which the user is comfortable. This would include such applications as using sounds to guide an individual through unknown territory if the person's vision and other senses are already monopolized by other inputs.

The Avatar Component

Another key element of The Communicator system will be avatars that can take on human appearance and behavior in a 3-D environment. They should be human-sized with full human fidelity, especially with respect to facial characteristics and emotion. The avatars should be able to assume any human form that is desired or most suitable (in terms of race, gender, and age, for example). The avatars' persona, mode of communication, and language should be able to be modified over time as the system learns the best method of communication or training for each individual.

The avatars should be life-like, so people will respond to them as though they are real. Avatars should be "in-a-box" and able to be placed and projected wherever needed, whether on a screen, as a hologram in the middle of a room, or through virtual reality viewers.

Possible applications include the following:

- Avatars could represent the human participants in a group to each other.
- They could also represent autonomous computerized agents that perform particular functions of the information and communication system.
- Avatars could be sent into dangerous situations, for example, to negotiate with a criminal holding a hostage.
- They could function as a resident nurse to the sick or as a companion to the elderly.
- An individual could perceive what his or her personal avatar encounters, e.g., "feeling" the presence of a biohazard or radiation in a dangerous environment while remaining immune to its harm.
- A training avatar (or a human tutor) could teach a person new skills by sharing the experience, for example, via a haptic suit, that could train a person in the physical movements required for dance, athletics, weaponry, or a refined manual skill such as surgery.

The Environmental Interface Component

A third key element of The Communicator system will be its interfaces with the surrounding "environmental network," creating the opportunity for enhanced,

personalized communications and education. Characteristics of how humans interact with information and technology can be viewed as constraints, or they can be viewed as strengths that convergent technology can play to. For example, if an individual is good at detecting anomalies or patterns in data, the technology would enhance this capability. Perhaps the technology would provide a "rheostat" of sorts to increase or decrease the contrast in data differences. This interface is a two-way street. The environment knows who is present, and each user receives appropriate information in the preferred form.

- The transforming strategy would apply known neural assessment techniques along with standard educational objectives, progressing to full cogno-assisted individualized learning in a group setting or collaborative learning.
- The system would be useful for teleconferencing, since participants need not be in the same location.
- The system should make it possible to adjust the social structure of communications, from whole-group mode in which all parties receive all messages, to more structured communication networks in which subgroups and individuals play specialized roles.

Key design considerations of The Communicator include the following:

- Very high-speed communications are needed, whether cable or wireless.
- The human-computer interface should be a wearable system offering augmented reality in office, schoolroom, factory, or field situations.

Educational Applications

All communication involves learning, but an *Educator* version of The Communicator could be created that would enhance many kinds of education. The convergence of NBIC technologies can radically transform the teaching and learning process and maximize the sensory and cognitive abilities of students. Some examples of applications include assistance to the learning disabled, optimally timed and individually presented learning experiences, and learning in a collaboratively orchestrated environment.

Several strategies could be employed to implement the Educator vision, geared for either individuals or groups, the classroom or the field. In the K-12 educational experience, a personal avatar or "coach" could govern hands-on experiments in accomplishing such goals as learning reading, science, math, or foreign languages. It would "teach" students as a human teacher does but would optimize itself to the needs of the student. It would be patient, friendly, stern, or take on any appropriate behavior. It might be most suitable for younger students but could also be a mentor for adults. If needed, it could be a "copilot." In a work environment, it could not only teach prepared lessons but also monitor performance and instruct on how to improve it.

The system could merge the following technologies:

- biotechnology to assess the physiological and psychological state of the learner, sense moods and states of mind
- cognitive science and technology to present responsive and individualized presentations of material to the student through different modalities

- expert information technology to accumulate and supply educational information

Military training could employ The Educator to teach decision-making under stress in a battlefield game in which the battlefield is virtual and the soldier is the general. As the war game is played, the avatar could be the general's assistant, read out after the battle. In another scenario, the virtual battlefield could be in a real field where soldier-participants wear wireless PDA helmets. The system could also be used as a "decision-making under stress" teaching tool for corporate executives.

Educator avatars could assume a wide variety of images (male, female, young, old) and be capable of speaking in all languages (oral and otherwise); identifying individual learning styles and then adapting curricula to individual needs and using access to biological data to determine which methods are most effective for the assimilation and retention of knowledge. This could effectively improve education and training in all arenas from preschool through graduate school and across the corporate and military environments. It would equalize educational opportunities for all, enable learners to move through material at their own pace, and ensure that knowledge of learning styles would be retained and carried forward from year to year as children move from teacher to teacher or adults move from job to job.

Social Equalization

The adaptive capabilities of The Communicator would have the potential in group interactions to minimize the biases that arise from a variety of factors such as physical size and posture, gender, race, language, culture, educational background, voice tone and volume, and physical ability or disability. The result would be to maximize both individual and group performance. Examples include enhancing the performance of a poor learner, an athlete, or a soldier, and improving communication, collaboration, and productivity among people with a multitude of differences. Thus, the system would be not only a Communicator and Educator, but an *Equalizer* as well, enhancing human awareness, removing disabilities, and empowering all members of society.

On a more fundamental level, such a smart device could have a tremendous impact on the most disadvantaged people around the world, those who lack clean drinking water, adequate food supplies, and so on. Despite the lack of physical infrastructure like telephone cables, wireless Communicator technology could offer them the world of information in a form they can immediately use. Such knowledge will improve their agricultural production, health, nutrition, and economic status. No longer isolated from the global economic and cultural system, they will become full and valued participants.

Convergence

The Communicator system will incorporate each of the four NBIC technologies:

- *Nanotechnology* will be required to produce high-speed computational capabilities, wearable components that consume little energy, and pervasive sensors.
- *Biotechnology* will be fundamental to the interfaces, to monitoring the physical status of participants, and to the general design of human-friendly technologies.

- *Information technology* will be responsible for data management and transmission, translation across modalities and languages, and development of avatars and intelligent agents.
- *Cognitive science* will provide the understanding of effective learning styles, methods for elimination of biases, and the directions in which to search for common values and ideas that will be the foundation of a new form of social cooperation.

Some elements of The Communicator can be created today, but the full system will require aggressive research across all four of the convergent NBIC fields. Implementation of the entire vision will require an effort spanning one or two decades, but the payoff will be nothing less than increased prosperity, creativity, and social harmony.

ENHANCED KNOWLEDGE-BASED HUMAN ORGANIZATION AND SOCIAL CHANGE

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Changes that bring together nanotechnology, information science, biology, and cognition have the potential to revolutionize the way we work and organize society. A large number of outcomes are possible. At the same time, existing social forms, legislation, and culture will limit and direct the potential outcomes. In a very real sense, technologies and societies, tools and cultures, capabilities and legislation will co-evolve. Without attempting to predict the future, a series of possible outcomes, issues, and research challenges are discussed. Particular emphasis is placed on issues of security and potentially radical change within groups, organizations, and society.

Data and Privacy

In the area of bioterrorism, a key issue is early detection or "biosurveillance." Early detection requires smart sensors at the biological level in the air, water, and ground and on humans. Early detection requires integrating this data with geographic, demographic, and social information. Even were the sensors to exist, there would still be a problem: Under current legislation and privacy laws, the data cannot be integrated and made readily accessible to practitioners and researchers. To develop and test data mining tools, knowledge management tools, and what-if policy simulators, access is needed to a wide range of data in real time; but, providing access to such data enables the users of these tools to "know" details of individual behavior.

In the area of organizations, a key issue is team design and redesign (Samuelson 2000). Team design and redesign requires accurate data of who knows what, can work with whom, and is currently doing what. Doing such a skill audit, network analysis, and task audit is a daunting task. Maintaining the information is even more daunting. Individuals are loathe to provide the information for fear of losing their basis of power or anonymity, or for fear of reprisal. However, much of the information is implicit in the locations that people occupy, their stress levels, webpages, curricula vitae, public conversations, and so on.

In the cases of both acquiring and maintaining individual data, all of the following can be used to enable better outcomes: nano-bio-sensors that are embedded in the body and that report on individual health, stress level, and location; intelligent surfaces that track who is present while reshaping themselves to meet the needs of and enhance the comfort of the users; auto-sensors that create a memory of what is said when people cough or sneeze; air and water sensors that sense contaminants; data-mining tools that locate information, simulation tools that estimate the change in social outcomes; information assurance tools and secure distributed databases. Indeed, such tools are critical to the collection, analysis, protection, and use of information to enhance group performance. The relatively easy problems here will be those that are dominated by technology, e.g., distributed database tools, data integration procedures, information assurance technology, and smart sensors. Those problems dealing with the need to change cultures, legislation, and ways of working will be more difficult. Privacy laws, for example, could mitigate the effectiveness of these tools or even determine whether they are ever developed. There are many critical privacy issues, many of which are well identified in the NRC report, *The Digital Dilemma* (http://www.nap.edu/catalog/9601.html). Views of knowledge as power will limit and impede data collection. Having such data will revolutionize healthcare, human resources, career services, intelligence services, and law enforcement. Having such data will enable "big-brotherism."

Were we able to overcome these two mitigating factors, then a key issue will become, "What will the bases for power be when knowledge is no longer a controlled commodity?" Since many organizations are coordinated and managed through the coordination and management of information, as knowledge is no longer controlled, new organizational forms should emerge. For example, a possible result might be the development of monolith corporations with cells of individuals who can do tasks, and as those tasks move from corporation to corporation, the cells would move as well. In this case, benefits, pay scales, etc., would be set outside the bounds of a traditional corporation. In this case, individual loyalty would be to the area of expertise, the profession, and not the company. Corporations would become clearinghouses linking agents to problems as new clients come with new problems.

Ubiquitous Computing and Knowledge Access

As computers are embedded in all devices, from pens to microwaves to walls, the spaces around us will become intelligent (Nixon, Lacey, and Dobson 1999; Thomas and Gellersen 2000). Intelligent spaces are generally characterized by the potential for ubiquitous access to information, people, and artificial agents, and the provision of information among potentially unbounded networks of agents (Kurzweil 1988). The general claim is that ubiquitous computing will enable everyone to have access to all information all the time. In such an environment, it is assumed that inequities will decrease. This is unlikely. While ubiquitous computing will enable more people to access more information more of the time, there will still be, short of major reforms, people with little to no access to computing. There will be excess information available, information making it difficult to discern true from false information. There will be barriers in access to information based on legislation, learning, and organizational boundaries. While information will diffuse faster, the likelihood of consensus being reached and being accurate given the information will

depend on a variety of other factors such as group size, the complexity of the task and associated knowledge, initial distribution of information in the group, and so on. As a result, things may move faster, but not necessarily better.

Initial simulation results suggest that even when there are advanced IT capabilities, there will still be pockets of ignorance, certain classes of individuals will have privileged access to information and the benefits and power that derive from that, groups will need to share less information to be as or more effective, databases may decrease shared knowledge and guarantee information loss, and smaller groups will be able to perform as well or better than larger groups (Alstyne, M. v., and Brynjolfsson, E. 1996; Carley 1999). To address issues such as these, researchers are beginning to use multiagent network models. These models draw on research on social and organizational networks (Nohira and Eccles 1992), advances in network methodology (Wasserman and Faust 1994), and complex system models such as multiagent systems (Lomi and Larsen 2001). In these models, the agents are constrained and enabled by their position in the social, organizational, and knowledge networks. These networks influence who interacts with whom. As the agents interact, they learn, which in turn changes with whom they interact. The underlying networks are thus dynamic. The results suggest that organizations of the future might be flatter, with individuals coming and going from teams based on skills, that is, what they know, and not whom they know. As a result, social life will become more divorced from organizational life. Initial simulation results suggest that if information moves fast enough, decisions will become based not as much on information as on the beliefs of others; this should be particularly true of strategic decisions.

Socially Intelligent Technology

Major improvements in the ability of artificial agents to deal with humans and to emulate humans will require those artifacts to be socially intelligent. Socially intelligent agents could serve as intelligent tutors, nannies, personal shoppers, etc. Sets of socially intelligent agents could be used to emulate human groups/organizations to determine the relative efficacy, feasibility, and impact of new technologies, legislation, change in policies, or organizational strategy. At issue are questions of how social these agents need to be and what is the basis for social intelligence. It is relatively easy to create artificial agents that are more capable than a human for a specific well-understood task. It is relatively easy to create artificial agents that can, in a limited domain, act like humans. But these factors do not make the agents generally socially intelligent. One of the research challenges will be for computer scientists and social scientists to work together to develop artificial social agents. Such agents should be social at both the cognitive and precognitive (bio) level. Current approaches here are software- limited. They are also potentially limited by data; nanotechnology, which will enable higher levels of storage and processing, will also be necessary. That is, creating large numbers of cognitively and socially realistic agents is technically unfeasible using a single current machine. Yet, such agents need to exist on a single machine if we are to use such tools to help individuals manage change.

A key component of social intelligence is the ability to operate in a multiagent environment (Epstein and Axtell 1997; Weiss 1999). However, not all multiagent

systems are composed of socially intelligent agents. For a machine to be socially intelligent, it needs to be able to have a "mental" model of others, a rich and detailed knowledge of realtime interaction, goals, history, and culture (Carley and Newell 1994). Socially intelligent agents need transactive memory, i.e., knowledge of who knows whom (the social network), who knows what (the knowledge network), and who is doing what (the assignment network). Of course this memory need not be accurate. For agents, part of the "socialness" also comes from being limited cognitively. That is, omniscient agents have no need to be social, whereas, as agents become limited — boundedly rational, emotional, and with a specific cognitive architecture — they become more social.

One of the key challenges in designing machines that could have such capabilities is determining whether such machines are more or less effective if they make errors like humans do. What aspects of the constraints on human cognition, such as the way humans respond to interrupts, the impact of emotions on performance, and so on, are critical to acquiring and acting on social knowledge? While we often see constraints on human cognition as limitations, it may be that social intelligence itself derives from these limitations and that such social intelligence has coordinative and knowledge benefits that transcend the limitations. In this case, apparent limits in individuals could actually lead to a group being more effective than it would be if it were composed of more perfect individual agents (Carley and Newell 1994).

A second key challenge is rapid development. Computational architectures are needed that support the rapid development of societies of socially intelligent agents. Current multiagent platforms are not sufficient, as they often assume large numbers of cognitively simple agents operating in a physical grid space as opposed to complex intelligent, adaptive, learning agents with vast quantities of social knowledge operating in social networks, organizations, and social space. Moreover, such platforms need to be extended to enable the co-evolution of social intelligence at the individual, group, and organizational level at differing rates and to account for standard human processes such as birth, death, turnover, and migration.

A third challenge is integrating such systems, possibly in real time, with the vast quantities of data available for validating and calibrating these models. For example, how can cities of socially intelligent agents be created that are demographically accurate, given census data?

Socially Engineered Intelligent Computer Anti-Viruses and DDOS Defenses

Computer viruses have caused significant financial losses to organizations (CSI 2000). Even though most organizations have installed anti-virus software in their computers, a majority of them still experience infections (ICSA 2000). Most anti-virus software can not detect a new virus unless it is patched with a new virus definition file. New virus countermeasures have to be disseminated once a new virus is discovered. Studies of viruses demonstrate that the network topology and the site of the initial infection are critical in determining the impact of the virus (Kephart 1994; Wang 2000; Pastor-Satorras 2001). What is needed is a new approach to this problem. Such an approach may be made possible through the use of socially intelligent autonomous agents.

The Web and the router backbone can be thought of as an ecological system. In this system, viruses prey on the unsuspecting, and distributed denial of service attacks (DDOS) spread through the networks "eating" or "maiming" their prey. Viruses are, in a sense, a form of artificial life (Spafford 1994). One approach to these attacks is to propagate another "species" that can in turn attack these attackers or determine where to place defenses. Consider a computer anti-virus. Computer anti-viruses should spread fixes and safety nets, be able to "eat" the bad viruses and restore the machines and data to various computers without, necessarily, the user's knowledge. Such anti-viruses would be more effective if they were intelligent and able to adapt as the viruses they were combating adapted. Such anti-viruses would be still more effective if they were socially intelligent and used knowledge about how people and organizations use computers and who talks to whom in order to assess which sites to infiltrate when. We can think of such anti-viruses as autonomous agents that are benign in intent and socially intelligent.

Social Engineering

Combined nano-, bio-, info-, and cogno-technologies make it possible to collect, maintain, and analyze larger quantities of data. This will make it possible to socially engineer teams and groups to meet the demands of new tasks, missions, etc. The issue is not that we will be able to pick the right combination of people to do a task; rather, it is that we will be able to pick the right combination of humans, webbots, robots, and other intelligent agents, the right coordination scheme and authority scheme, the right task assignment, and so on, to do the task while meeting particular goals such as communication silence or helping personnel stay active and engaged. Social engineering is, of course, broader than just teams and organizations. One can imagine these new technologies enabling better online dating services, 24/7 town halls, and digital classrooms tailored to each student's educational and social developmental level.

The new combined technologies are making possible new environments such as smart planes, "living" space stations, and so on. How will work, education, and play be organized in these new environments? The organizational forms of today are not adequate. Computational organization theory has shown that how groups are organized to achieve high performance depends on the tasks, the resources, the IT, and the types of agents. You simply do not coordinate a group of humans in a board room in the same way that you would coordinate a group of humans and robots in a living space station or a group of humans who can have embedded devices to enhance their memory or vision.

Conclusion

These areas are not the only areas of promise made possible by combining nano-, bio-, info-, and cogno-technologies. To make these and other areas of promise turn into areas of advancement, more interdisciplinary research and training is needed. In particular, for the areas listed here, joint training is needed in computer science, organizational science, and social networks.

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A VISION FOR THE AIRCRAFT OF THE 21ST CENTURY

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The airplane will soon be 100 years old. Over that period of time, it has evolved from the cloth and wood biplanes of the 1920s to the first all-metal single-wing aircraft of the 1930s, to the 100-passenger commercial transports of the 1950s, to the modern jet aircraft capable of reaching any point in the world in a single day. Nevertheless, the design of the modern airplane really has not changed much in the last 50 years. The grandfather of the Boeing 777 was the Boeing B-47 bomber designed in the late 1940s. It had a sleek, tubular aluminum fuselage, multiple engines slung under swept wings, a vertical tail, and horizontal stabilizers. Today, the fuselage is lighter and stronger, the wings more aerodynamic, and the engines much more efficient, but the design is a recognizable descendent of the earlier bomber.

The aircraft of the 21st century may look fundamentally different (Figure D.3). NASA is beginning to look to birds as an inspiration for the next generation of aircraft — not as a "blueprint," but as a biomimetic mode (Figure D.4). Birds have evolved over the ages to be totally at home in the air. Consider our national bird, the eagle. The eagle has fully integrated aerodynamic and propulsion systems. It can morph and rotate its wings in three dimensions and has the ability to control the air flow over its wings by moving the feathers on its wingtips. Its wings and body are integrated for exceptional strength and light weight. And the wings, body, and tail

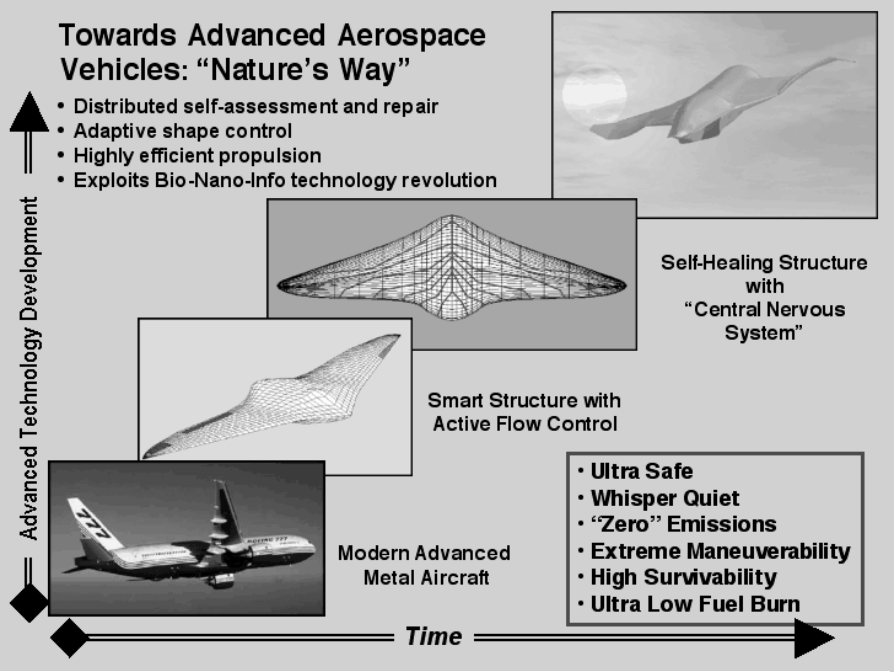

Figure D.3. Towards advanced aerospace vehicles: "Nature's Way."

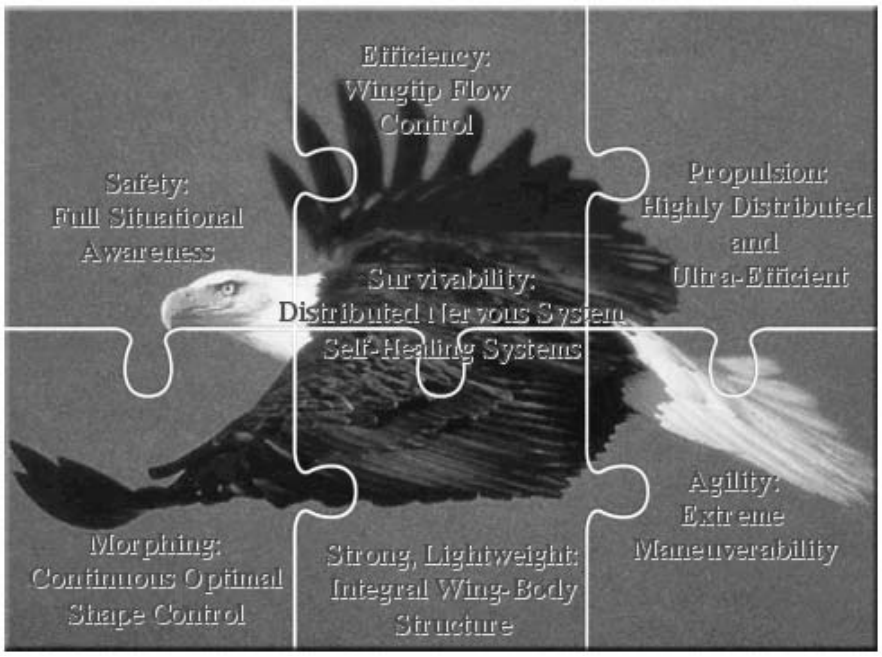

Figure D.4. Inspiration for the next generation of aircraft.

work in perfect harmony to control aerodynamic lift and thrust and balance it against the force of gravity. The eagle can instantly adapt to variable loads and can see forward and downward without parallax. It has learned to anticipate the sudden drag force on its claws as it skims the water to grab a fish and how to stall its flight at just the right moment to delicately settle into a nest on the side of a cliff. The eagle is made from self-sensing and self-healing materials. Its skin, muscle, and organs have a nervous system that detects fatigue, injury, or damage, and signals the brain. The eagle will instantly adapt to avoid further trauma, and tissues immediately begin to self-repair. The eagle is designed to survive.

NASA is pursuing technology today that is intended to lead toward just such a biomimetically inspired aircraft (Figure D.5). Advanced materials will make them lighter and more efficient to build. Advanced engines will make them fast and efficient. The airframe, engine, and cockpit will be "smarter." For decades, aircraft builders have worked to build wings that are stronger and stiffer. However, the wing that is needed for take-off and landing is not the wing needed for cruising. During take-off and landing, the wing needs to be highly curved from leading edge to trailing edge to produce enough lift at low speed. But this also produces a lot of drag. Once airborne, the wing needs to be flat for minimal drag during cruise. To change the wing shape, NASA has employed leading-edge slats — an articulated "nose" that runs along the length of the wing — and multipiece flaps that can drop the trailing edge of the wing by 60 degrees. All of this requires gears, motors, and hydraulic pumps.

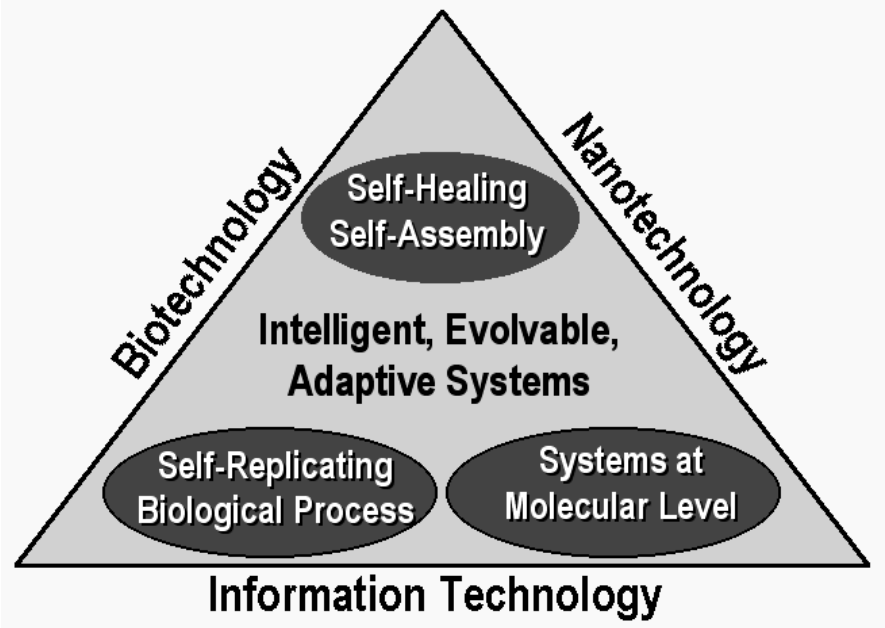

Figure D.5. Revolutionary technology vision as applied to future aircraft.

Imagine a bird-like wing of the future. It is not built from multiple, mechanically connected parts. It is made from new smart materials that have imbedded sensors and actuators — like nerves and sinew. The sensors measure the pressure over the entire surface of the wing and signal the actuators how to respond. But even the sensors are smart. Tiny computing elements detect how the aircraft responds to sensor signals. They eventually learn how to change the shape of the wing for optimal flying conditions. They also detect when there is damage to a wing and relay the extent and location to the pilot. And, like an injured bird, the wing adjusts its response to avoid further damage. This will not only be a very efficient and maneuverable airplane, but a very safe one.

Like the wings, the engines of this plane have integral health-management systems. Temperatures, pressures, and vibrations are all continuously monitored and analyzed. Unique performance characteristics are automatically developed for each engine, which then continually operates as efficiently as possible, and very safely. Long before a part fails, damage is detected and protective maintenance scheduled.

Inside the cockpit compartment, the pilot sees everything on a 3-D display that shows local weather, accentuates obstacles, all near-by aircraft, and the safest flight path. The on-board clear air turbulence sensor uses lasers to detect unsteady air well ahead of the aircraft to assure a smooth ride. When approaching a major airport, the lingering vortices that were shed from the wingtips of larger aircraft and that can upset a smaller one, can be easily avoided. This is a long-term vision, but emerging technology can make it real.

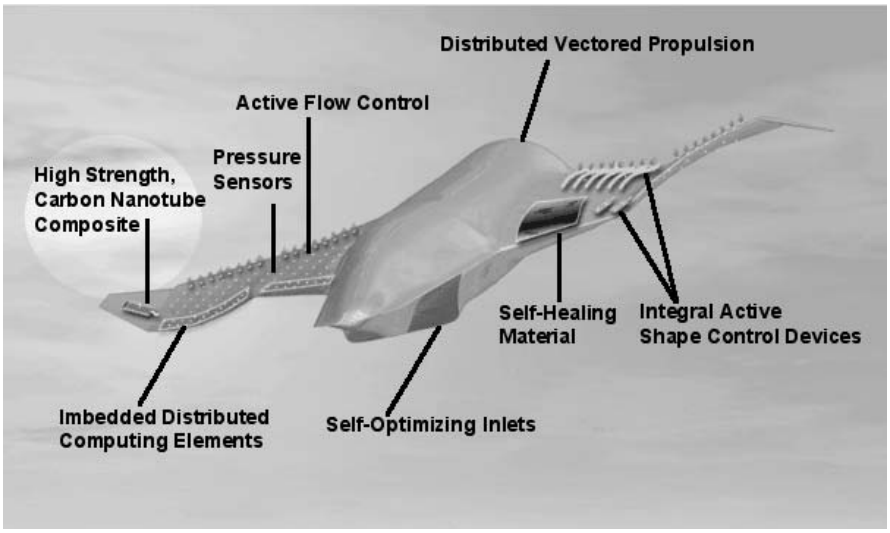

Figure D.6. NASA's dream of a future flight vehicle.

A key to achieving this vision is a fusion of nanoscale technology with biology and information technology (Figure D.6). An example is intelligent multifunctional material systems consisting of a number of layers, each used for a different purpose. The outer layer would be selected to be tough and durable to withstand the harsh space environment, with an embedded network of sensors, electrical carriers, and actuators to measure temperature, pressure, and radiation and to trigger a response whenever needed. The network would be intelligent. It would automatically reconfigure itself to bypass damaged components and compensate for any loss of capability. The next layer could be an electrostrictive or piezoelectric membrane that works like muscle tissue with a network of nerves to stimulate the appropriate strands and provide power to them. The base layer might be made of biomolecular material that senses penetrations and tears and flows into any gaps. It would trigger a reaction in the damaged layers and initiate a self-healing process.

Carbon nanotube-based materials are an example of one emerging technology with the potential to help make this a reality. They are about a hundred times stronger than steel but one-sixth the weight of steel. They can have thermal conductivities seven times higher than the thermal conductivity of copper with 10,000 times greater electrical conductivity. Carbon nanotube materials may also have piezoelectrical properties suitable for very high-force activators. Preliminary NASA studies indicate that the dry weight of a large commercial transport could be reduced by about half compared to the best composite materials available today. The application of high-temperature nanoscale materials to aircraft engines may be equally dramatic. Through successful application of these advanced lightweight materials in combination with intelligent flow control and active cooling, thrust-to-weight ratio increases of up to 50 percent and fuel savings of 25 percent may be possible for conventional engines. Even greater improvement can be achieved by developing vehicle designs that fully exploit these materials. This could enable vehicles to smoothly change their aerodynamic shape without hinges or joints.

Wings and fuselages could optimize their shape for their specific flight conditions (take-off, cruise, landing, transonic, and high-altitude).

In the long-term, the ability to create materials and structures that are biologically inspired provides a unique opportunity to produce new classes of self-assembling material systems without the need to machine or process materials. Some unique characteristics anticipated from biomimetics are hierarchical organization, adaptability, self healing/self-repair, and durability. In the very long term, comparable advances in electrical energy storage and generation technology, such as fuel cells, could completely change the manner in which we propel aircraft. Future aircraft might be powered entirely electrically. In one concept, thrust may be produced by a fan driven by highly efficient, compact electric motors powered by advanced hydrogen-oxygen fuel cells. However, several significant technological issues must still be resolved in order to use hydrogen as a fuel, such as efficient generation and storage of hydrogen fuel and an adequate infrastructure necessary for delivering the fuel to vehicles (Figure D.7).

None of this is expected to happen quickly. Over the next decade we will likely see rapid development of advanced multifunctional, nanotechnology-based structural materials, such as carbon nanotube composites. Integrated health monitoring systems — for airframe and engine — may be developed, and deformable wings with imbedded actuators may also be developed. The cockpit will likely begin to become more of an extension of the pilot with greater use of senses other than sight to provide "situational awareness" of the aircraft and its operating environment. In two to three decades, we may see the first "bio/nano/thinking/sensing" vehicles with significant use of nanotechnology-based materials, fully integrated exterior-interior flow control, and continuously deformable wings. By then, the aircraft may also have a distributed control/information system — like a nervous system — for health monitoring, some level of self-repair, and cockpits that create a full sensory, immersive environment for the pilot.

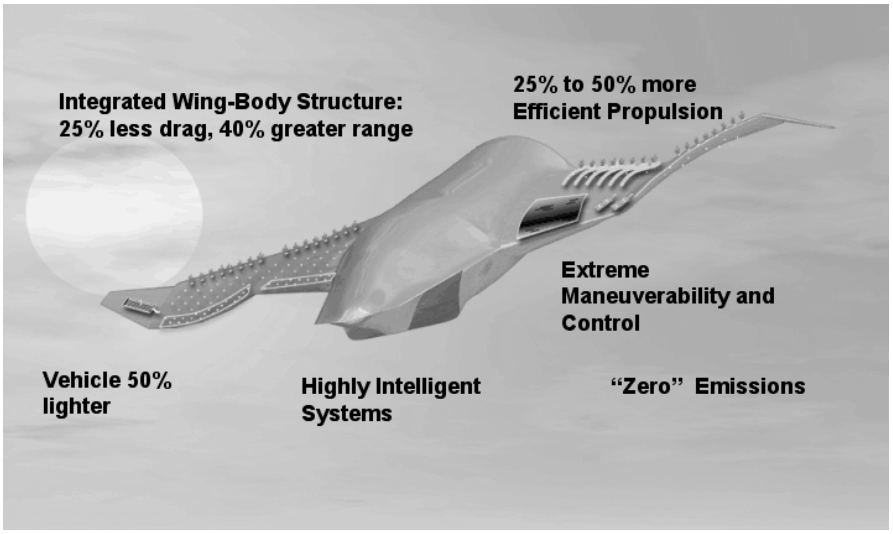

Figure D.7. Attributes of a future flight vehicle.

MEMETICS: A POTENTIAL NEW SCIENCE

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In the "information society" of the 21st century, the most valuable resource will not be iron or oil but culture. However, the sciences of human culture have lacked a formal paradigm and a rigorous methodology. A fresh approach to culture, based on biological metaphors and information science methodologies, could vastly enhance the human and economic value of our cultural heritage and provide cognitive science with a host of new research tools. The fundamental concept is the *meme*, analogous to the gene in biological genetics, an element of culture that can be the basis of cultural variation, selection, and evolution.

The meme has been characterized both as a concept that could revolutionize the social sciences as the discovery of DNA and the genetic code did for biology, and as a concept that cannot produce a general theory of social evolution because requirements for Darwinian evolution do not map into the social domain (Aunger 2000). There is a lot we do not understand about human behavior in groups, its relation to learning, cognition, or culture. There is no general theory that situates cognition or culture in an evolutionary framework, Darwinian or otherwise. It is also hard to conduct science in the social domain, not just because it is difficult to conduct experiments, but also because it is difficult to be objective. Prior efforts to "Darwinize" culture have a long and ignoble history. The question naturally arises as to what is new that might allow progress this time around, or should discretion take the better part of valor?

While any debate tends to sharpen the debate issues, in this case it may prematurely close off a search for a scientific definition of important terms and of an appropriate contextual theory. For example, a strictly Darwinian approach to cultural or social evolution may not be appropriate since humans can learn concepts and, in the same generation, pass them on to their offspring. Because memes are passed from one individual to another through learning, characteristics an individual acquires during life can be transmitted to descendents. This is one of the reasons why memes may evolve more rapidly than genes. In the language of historical debates in biology, culture appears to be Lamarckian, rather than Darwinian (Strong 1990). This would imply a different set of requirements for an evolutionary system that are not yet well understood.

As another example, we are only now discovering that many of the genes of an organism code for "chaperone" proteins that do not have "meaning" in a particular biological function, but, rather, play a role in molecular recycling and enabling the proteomic networks of molecules to interact in an orderly fashion (Kim et al. 1998). We do not yet understand how a balance is kept within a cell between the evolutionary need for variety and the need to preserve order in systems. Nevertheless, it is likely that in a fast-changing Lamarckian system, such processes become even more important. On the socio-cultural level, religious ideologies appear to have chaperone roles that may help keep individuals focused on important daily activities rather than getting caught up in unsolvable dilemmas and becoming

[2] The views in this essay do not necessarily represent the views of the National Science Foundation.

unable to act. Even so, such ideologies cannot become so strict as to eliminate important variety from an evolutionary system. This tradeoff between order and disorder may operate like a regulator for social change (Rappaport 1988).

While there is no known Federal grants program focused on memetics, nor any apparent, organized research community, there are likely a number of existing and completed research projects that impact on the domain. These probably are found in a variety of disciplines and do not use a common vocabulary. For example, a few archaeologists apply evolutionary theory in their work (Tschauner 1994; Lyman and O'Brien 1998), and some cultural anthropologists explore the evolution of culture in a context that is both social and biological (Rindos 1985; Cashdan 2001; Henrich 2001). However, most archaeologists avoid theoretical explanations altogether, and cultural anthropology is currently dominated by a humanist rather than a scientific paradigm. So, even though starting a research program in this area would not have to begin from scratch, there would be much work to do. The biggest roadblock would be getting researchers from various disciplines to collaborate over a common set of interests.

At a first approximation, there are three different realms in which biological genetics is valuable to humanity. First, it contributes to the progress of medicine, because there is a genetic aspect to all illnesses, not only to those diseases that are commonly labeled "genetic" or "inherited." Second, it provides valuable tools for agriculture, most recently including powerful techniques of genetic engineering to design plants and animals that are hardier, more nutritious, and economically more profitable. Third, it answers many fundamental scientific questions about the nature and origins of biological diversity, thus contributing to human intellectual understanding of ourselves and the world we live in. Cultural memetics would have three similar realms of applications, as described below.

Cultural Pathology

Culture is not just art, music, language, clothing styles, and ethnic foods. Importantly, it also includes the fundamental values, norms, and beliefs that define a society's way of life. Thus, the classic problem of social science has been to understand how and why some people and groups deviate from the standards of society, sometimes even resorting to crime and terrorism. Recent attention on closed groups has once again raised the question, "Why do people believe weird things?" — to borrow from a recent book title (Schermer 2002). The problem of social order thus depends upon the dynamic interactions between cultures, subcultures, and countercultures.

For decades, various anthropologists have considered whether or not there is a cultural equivalent of the human genome underlying differences of belief and behavior across groups or whether cultural context differentially expresses elements from a common repertoire available to all humans. One way to approach the issue might be to study culture with methodologies similar to those of bioinformatics.

A key bioinformatics construct is the genomic code, the cultural equivalent of which has been widely discussed under the concept of "meme" (Dawkins 1976). Cross-cultural signals are often undetected or misidentified, and cultural miscommunication is commonplace, leading one to suspect the existence of such codes and their differentiation among social groups. Levi-Strauss (1966) refers to

cultural concepts, or artifacts, as "things to think with." Such shared concepts may, however, be more a form of externalized representation, or "cognitive Post-It Notes," with important information processing functionality for a social group.

The prevalence of fundamentalist cultural and religious movements, for example, suggests that there may be an equivalent of the "auto-immune" response at the cultural level. Religion appears to be what Talcott Parsons (1964) called an "evolutionary universal," essential to the functioning of societies and prominent in every long-lasting culture. Within the realm of religion, diversification also appears to be universal, and it may be vain to hope that all people can eventually come to share compatible religious beliefs (Stark and Bainbridge 1987). At the present time, it is crucial to understand that revitalization or nativistic movements appear to be universal in times of great social change (Wallace 1956). Such movements tend toward increased orthodoxy and the involvement of charismatic leaders. Anthropologists have studied such movements from the time of the "Ghost-Dance" cults of native North Americans at the end of the 19th century to the rise of militant groups in Islam today (La Barre 1972).

"World-views" may be self-regulating, in this respect, each dominant ideology naturally stimulating the evolution of counter-ideologies. Just when Western Civilization rejoiced that it had vanquished Nazism and Marxism, and the "end of history" was at hand, radical Islam emerged to challenge its fundamental values (El-Affendi 1999). Quite apart from the issue of terrorist attacks from radical fringes of Islam, the entire Muslim religious tradition may have an evolutionary advantage over western secularism, because it encourages a higher birth rate (Keyfitz 1986). An inescapable natural law may be at work here, comparable to that which regulates the constantly evolving relations between predators and prey in the biological realm, ensuring that there is always a rival culture, and complete victory is impossible (Maynard Smith 1982). However, deep scientific understanding of the memetic processes that generate radical opposition movements may help government policymakers combat them effectively. It may never be possible to eradicate them entirely, but with new scientific methods, we should be able to prevent them from driving our civilization to extinction.

A science of memetics, created through the convergence of many existing disciplines, would likely give a basis for understanding the relationship between social groups and globalization — a topic of enormous recent interest. Fundamentalist groups are no longer "fringe" as they practice tactics to deal with variety and change, and they have become a topic not only for cultural anthropologists but also for law enforcement and governments in general. Certain "ideas" may have the force of a social virus that spreads as quickly and can have as deleterious effects on a population as do biological viruses (Boyd and Richerson 1985; Dennett 1995; Sagan 1997). It is important to examine such theories and to consider whether or not people are naturally vulnerable to "hacking" in the concept domain, as their computer networks are vulnerable in cyberspace. At the same time, memetics can help us understand the forces that promote cooperation between people and sustain culturally healthy societies (Axelrod 1990).

Memetic Engineering

Since long before the dawn of history, human beings have influenced the evolution of plants and animals, by domesticating them, breeding them, and now by engineering their genetic structure directly (Diamond 1997). Over the same span of millennia, humans became progressively more sophisticated in the processes by which they generate and transmit new culture, leading to the advanced electronic media of today. However, while agriculture in recent centuries has employed genetic science and technology of advancing complexity to domesticate plants and animals, the culture-based industries have not yet made use of memetic science.

It is important to realize that the term *culture* is defined very broadly by anthropologists and other social scientists. It is not limited to high artistic culture (symphonies, oil paintings, and great poetry), popular culture (rock music, best-selling novels, and dress styles), or intellectual culture (academic philosophies, schools of scholarship, and scientific theories). It also includes the practices of skilled professions, from surgery to litigation, financial accounting to bridge building, dentistry to uranium mining, and from auto mechanics to rocket science. The habitual patterns of behavior in families, neighborhoods, corporations, and government agencies are also forms of culture. We can say that culture refers to any pattern of thought and behavior that is shared through learning, rather than being rooted in biological inheritance.

We take for granted the assumption that government agencies like the National Science Foundation, National Institutes of Health, Defense Advanced Research Projects Agency, and Department of Energy should conduct fundamental scientific research that will ultimately be of benefit to manufacturing and transportation industries and to the military. At the same time, debates range over how heavily government should be involved in supporting culture through agencies like National Endowment for the Arts or National Endowment for the Humanities. But here we are discussing something very different from grants to support the work of artists and humanists. Rather, we refer to fundamental scientific research on the dynamics of culture, that will be of benefit to culture-creating and communication industries, and to national security through relations with other countries and through an improved ability to deal successfully with a wide range of nongovernmental organizations and movements.

If manufacturing creates the hardware of modern economies, the culture industries create the software. Both are essential to prosperity, and in the modern world, both should be grounded in solid scientific knowledge. If we understood better how human beings actually innovate, whether in music or the engineering design of consumer products, we could help them do it better. If we had a better map of culture, analogous to the Linnean system that classifies biological organisms into species and genera, we could help people find the culture they want and we could locate “uninhabited” cultural territories that could profitably be colonized by growing industries. Many of the social problems faced by contemporary American society seem to have substantial cultural aspects, so the findings of scientific memetics would be extremely valuable for both the government agencies and private organizations that have to deal with them.

As the Human Genome Project drew to its conclusion, it became clear to everyone that “mapping the human genome” was only part of the work. Also

necessary was studying the great genetic diversity that exists from person to person around the planet, and discovering the biochemical pathways through which each gene was expressed in the phenotypic characteristics of the individual. Comparable work will be required in cultural memetics. For any given cultural trait, there may exist a number of distinct alternatives, like alleles in biological genetics, the mutational forms of a gene. The characteristics of varied individuals are the complex result of different alleles interacting across numerous genes. Categorization of culture from a memetic perspective will identify these alleles, and memetic engineering could make extensive use of techniques for combining these cultural traits in new ways (Bainbridge 1985).

Understanding how memes are expressed in actual human behavior will require advances in cognitive science that will have spin-off benefits in education and the culture industries. For example, research on how language is encoded both memetically and cognitively will contribute to better language instruction in schools and more effective commercial and governmental translation across languages. As in any major scientific endeavor, there may be a large number of unexpected benefits, but the gains we can identify now already more than justify the development of memetic science on economic grounds alone.

A Science of Culture

Participants in the Convergent Technologies (NBIC) conference recommended a new scientific initiative, analogous to the Human Genome Project that charted the human genetic code, which they called the Human Cognome Project — unraveling the secrets of the human cognitive genome. Any attempt to solve the riddles of the human mind will have to be far more than an exercise in brain neurology; most importantly, it will have to attack the mysteries of the cultural genome.

One major benefit of a program in memetics would be to better understand culture as an evolutionary process in its own context, whether as a Darwinian, Lamarckian, or as yet unknown system (Boyd and Richerson 1985). The knowledge gained could create a framework for a scientific rebirth in social and cultural domains. While opinions vary, it would not be too harsh to suggest that several social sciences seem to have stalled, some of them achieving very little progress in recent decades. The same thing occasionally happens in physical sciences. For example, planetary astronomy had practically stalled in the two or three decades prior to the launch of the first interplanetary space probes. Similarly, cancer research has achieved progress only very slowly over the past century, but the Human Genome Project offers new hope of breakthroughs. Memetic science could provide just the intellectual boost and potent research methodology needed by such diverse fields as Anthropology, Political Science, and Sociology.

Development of new theories and methods will require cooperation between hundreds of scientists in perhaps a dozen fields, so here with our limited perspectives we can suggest only a few of the possibilities. Perhaps there are a number of common features of natural codes, including both cultural and biological codes:

- *The "independence" feature*: Natural code elements tend to have arbitrary meaning (C.S. Peirce's symbols, as opposed to icons or indices) facilitating abstraction and reuse.

- *The "combinatorial advantage" feature*: The number of potential representations is much larger in combinations of elements than in one-to-one element coding — perhaps because evolutionary selection favors representational richness available by combination sets.
- *The self-regulation of natural codes*: Dependency upon a code results in a constraint for new input to be interpreted in terms of the code; change is thereby limited to evolution of the code over time.

Work on applying language modeling to genomic sequences at Carnegie Mellon University has suggested that genomes differentiate species by having distributions that include rare occurrences and where such rare occurrences can often be species-unique. This work suggests that some species-unique sequences have an unusual generative power, such as those playing an important role in fold initiation of proteins. Perhaps cultural codes also contain some rare occurrences that serve to differentiate cultures and are heavily associative, or generative, within the culture.

The study of cultural codes, such as suggested here, has not proceeded as rapidly as other fields such as bioinformatics. Perhaps there are reasons of politics and objectivity that have lowered the expectation of resources available for doing such research. Cultural codes may be easier and more politically feasible to study in the short-run in culturally primitive groups or other large-brained species. Bottlenose dolphins, for example, participate in fluid, short-term social associations, and their vocal plasticity as well as their behavior appears to be related to their fission/fusion social structure (Reiss et al. 1997). Perhaps dolphins' fluid social groups provide external cognitive representations (perhaps via "mirror neurons") in a manner similar to the totems of primitive human cultural groups.

Several systematic research methodologies need to be developed. One breakthrough that seems within reach would be the memetic equivalent of the Linnean system for classifying species, genera, and other kinds of biological clades. In recent years, information science has developed a range of techniques, such as latent semantic analysis and semantic concept space technology (Harum et al. 1996). United with cognitive science, these methods should go a long way to identifying the structure of the cultural genome and the mechanisms by which it changes or sustains itself. Through the development of memetic science, we will want to look to genetics for inspiration and selectively import both theories and methods from biology when appropriate.

The scientific study of culture is both possible and pregnant with knowledge of human behavior. Thus, it deserves to be given more resources, especially in light of current events. These events include not only the terrorism of September 11, 2001, but also the dot-com crash and the failure of nations as diverse as Argentina, Indonesia, and Japan to sustain their economic development. Memetic science could help us deal with challenges to American cultural supremacy, discover the products and services that will really make the information economy profitable, and identify the forms of social institutions most conducive to social and economic progress.

A Transforming Strategy

The most obvious barrier to the emergence of a successful science of memetics is the lack of a unified scientific community to create it. We suggest that three kinds of major projects would be needed to establish the nucleus for this vital new field:

1. *Professional conferences, scientific journals, and a formal organization devoted to memetics.* A scientific community needs communication. Because memetics spans biology, information science, cognitive science, and cultural studies, the people who will create it are strewn across many different disciplines that hold their annual meetings at different times in different cities. Thus, a series of workshops and conferences will be essential to bring these people together. Out of the conferences can emerge publications and other mechanisms of communication. An electronic communication network at the highest level of scientific quality needs to be established.
2. *Data infrastructure, in the form of multiuse, multiuser digital libraries incorporating systematic data about cultural variation, along with software tools for conducting scientific research on it.* Some work has already been accomplished of this kind, notably the decades-long efforts to index the findings of cultural anthropological studies of the peoples of the world, accessible through World Cultures Journal (http://eclectic.ss.uci.edu/ ~drwhite/ worldcul/world.htm), and cross-cultural questionnaire surveys such as The World Values Survey (http://wvs.isr.umich.edu/). However, existing data were not collected with memetic analysis in mind. They typically ignore most dimensions of modern cultures, and they lack information about the networks of communication between individuals and groups that are fundamental to memetic mutation and diffusion. Thus, entirely new kinds of cultural data infrastructure are needed, to provide the raw material for memetic science.
3. *Specific major research projects assembling multidisciplinary teams to study distinct cultural phenomena that are most likely to advance fundamental memetic science and to have substantial benefits for human beings.* Because culture is highly diverse, it is essential to support multiple projects in different domains. This strategy would connect data infrastructure projects with teams of scientists oriented toward answering specific but profound scientific questions. One recent suggestion that has merit on both scientific and practical grounds is to create an distributed digital library devoted to all aspects of Islamic culture, with special attention to understanding how it evolves and divides. Another worthwhile project would be to link existing linguistic data archives, for example represented by the Linguistic Data Consortium, then transform them into a laboratory for studying the constant process of change that goes on within and across languages. A very different project, with a wide range of intellectual and economic benefits, would be an institute to study the transformation of engineering and manufacturing by the development of nanotechnology, gaining fundamental scientific understanding of the innovation process, to improve the methods by which new technologies are developed.

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E. NATIONAL SECURITY

THEME E SUMMARY

Panel: R. Asher, D.M. Etter, T. Fainberg, M. Goldblatt, C. Lau, J. Murday, W. Tolles, G. Yonas

The fourth NBIC theme examines the ways in which the United States and modern civilization can meet the intelligence and defense challenges of the new century. In a world where the very nature of warfare is changing rapidly, national defense requires innovative technology that (a) projects power so convincingly that threats to the United States are deterred, (b) eliminates or minimizes the danger to U.S. warfighters from foe or friendly fire, and (c) reduces training costs by more than an order-of-magnitude through augmented reality and virtual reality teaching aids.

Investment in convergent nanotechnology, biotechnology, information technology, and cognitive science is expected to result in innovative technologies that revolutionize many domains of conflict and peacekeeping. We are entering an era of network-centric combat and information warfare. Increasingly, combat vehicles will be uninhabited, and robots or other automated systems will take on some of the most hazardous missions. Effective training will make extensive use of augmented or virtual reality. Nanotechnology will offer reliable means for detecting and protecting against chemical and biological agents. Convergence of many technologies will enhance the performance of human warfighters and defenders, in part through monitoring health and instituting prophylaxis and through magnifying the mental and physical capabilities of personnel.

The Defense Science and Technology Strategy (Department of Defense 2000) seeks to ensure that the warfighters today and tomorrow have superior and affordable technology to support their missions and to give them revolutionary war-winning capabilities. There is special focus on information assurance with emphasis on security; battlespace awareness with emphasis on sensor webs, miniaturized platforms, netted information, and cognitive readiness; force protection with emphasis on chemical/biological defense; and support for the warfighter.

In the recent past, new technologies have dramatically enhanced American ability to both prepare for and execute military actions. By implementing advances in information technologies, sensors, and simulation, we have strengthened our ability to plan and conduct military operations, quickly design and produce military systems, and train our forces in more realistic settings. These technologies are central to greater battlefield awareness, enabling our forces to acquire large amounts of information, analyze it quickly, and communicate it to multiple users simultaneously for coordinated and precise action. As former Defense Secretary William J. Perry has noted, these are the technological breakthroughs that are "changing the face of war and how we prepare for war."

Numerous special programs, reports, and presentations address these goals. The Department of Defense has designated nanoscience as a strategic research area in order to accelerate the expected benefits (Murday 1999). Various conferences and

studies have been devoted to assessing nanotechnology status and needs for defense (Murday 2000; National Research Council, forthcoming). Attention has also been paid to anticipating more global societal consequences of those efforts in support of national security (Roco and Bainbridge 2001).

National Security Goals for NBIC

This conference panel identified seven goals for NBIC augmentation of national security, all of which require the close integration of several of the nanotechnology, biotechnology, information technology, and cognition fields of endeavor. The seven goals, listed below, are sufficiently diverse that there is no common strategy beyond the need for interdisciplinary integration. The net result of accomplishing the stated goals would reduce the likelihood of war by providing an overwhelming U.S. technological advantage, would significantly reduce the cost of training military manpower, and would significantly reduce the number of lives lost during conflict.

1. **Data linkage, threat anticipation, and readiness.** Miniaturized, affordable sensor suites will provide information from previously inaccessible areas; high-speed processing will convert the data into information; and wide-bandwidth communication pipelines with digital security will distribute information rather than data to all who need it.
2. **Uninhabited combat vehicles.** Automation technology (including miniaturization of sensing, augmented computation and memory, and augmented software capability) will enable us to replace pilots, either fully autonomously or with pilot-in-the-loop, in many dangerous warfighting missions. The uninhabited air vehicle will have an artificial brain that can emulate a skillful fighter pilot in the performance of its missions. Tasks such as take-off, navigation, situation awareness, target identification, and safe return landing will be done autonomously, with the possible exception of circumstances requiring strategic or firing decisions. Without the human g-force constraint and the weight of human physical support equipment (oxygen, ejection system, armor, etc.), the planes will be more maneuverable. Tanks, submarines, and other combat vehicles will experience similar benefits.
3. **Warfighter education and training.** A partnership between nanotechnology and information technology holds the promise for relatively inexpensive, high-performance teaching aids. One can envision a virtual-reality teaching environment that is tailored to the individual's learning modes, utilizes contexts stimulating to that individual, and reduces any embarrassment over mistakes. The information exchange with the computer can be fully interactive, involving speech, vision, and motion. Nanodevices will be essential to store the variety of necessary information and to process that information in the millisecond time frames necessary for realtime interaction.
4. **Chemical/biological/radiological/explosive (CBRE) detection and protection.** Microfabricated sensor suites will provide ample, affordable, error-free forewarning of chemical, biological, radiological, or explosive threat. For those who must work in a contaminated environment, individual protection (masks and clothing) will induce heat stresses no greater than conventional uniforms while providing full protection. Decontamination and

neutralization procedures will be effective against agents, yet will be relatively benign to people and the environment. Monitors will provide information on warfighter physiological status and initiate any necessary prophylaxis.

5. **Warfighter systems.** The warfighter is subjected to periods of intense stress where life or death decisions must be made with incomplete information available, where the physiology of fatigue and pain cloud reason, and where supplemental technology must compete with the 120 pounds of equipment weight s/he must carry. NBIC technologies can address all of these aspects of warfighting. Nanotechnology holds the promise to provide much greater information, connectivity, and risk reduction to the warfighter. The continued miniaturization of electronic devices will provide 100 times more memory with less bulk and weight (a terabit of information in a cm^2). Processing speeds will increase to terahertz rates. Displays will be flexible and paper-thin, if not replaced by direct write of information on the retina. High-bandwidth communication will be netted. Prolific unattended sensors and uninhabited, automated surveillance vehicles under personal warfighter control will be providing high data streams on local situations. Weapons will automatically track targets and select precise firing times for greater accuracy. The marriage of semiconductors and biology will provide physiological monitors for alertness, chemical or biological agent threats, and casualty assessment. The small size of the nanodevices will limit the volume, weight, and power burdens.
6. **Non-drug treatments for enhancement of human performance.** Without the use of drugs, the union of nanotechnology and biotechnology may be able to modify human biochemistry to compensate for sleep deprivation and diminished alertness, to enhance physical and psychological performance, and to enhance survivability rates from physical injury.
7. **Applications of brain-machine interface.** The convergence of all four NBIC fields will give warfighters the ability to control complex entities by sending control actions prior to thoughts (cognition) being fully formed. The intent is to take brain signals (nanotechnology for augmented sensitivity and nonintrusive signal detection) and use them in a control strategy (information technology), and then impart back into the brain the sensation of feedback signals (biotechnology).

Statements and Visions

Defense applications are intended for the highly competitive environments of deterrence, intelligence gathering, and lethal combat, so it is essential to be technologically as far ahead of potential opponents as possible. The United States and its closest allies represent only a small fraction of the world population, and in the asymmetrical conflicts of the early 21^{st} century, even a small number of dedicated enemies can cause tremendous damage. Thus, the overview statements and future visions written by participants in the national security working group address very high-priority areas where the United States and its allies can achieve and maintain great superiority. The statements and visions cover areas from enhancing soldier performance (M. Goldblatt) and combat readiness (D.M. Etter) to

future roles of NBIC for fighting terrorism (J. Murday, T. Fainberg, C. Lau) and equipping soldiers (R. Asher, J. Murday, T. Fainberg, C. Lau).

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STATEMENTS

COGNITIVE READINESS: AN IMPORTANT RESEARCH FOCUS FOR NATIONAL SECURITY

Delores M. Etter, United States Naval Academy

Cognitive readiness is a critical research area for the Department of Defense. Soldiers must not only be ready physically for the myriad of roles that they have in the world today, but they must also be ready cognitively. This cognitive readiness extends from handling stress and sleep deprivation, through training "anytime, anyplace," through additional information provided by augmented reality, and through realtime physical monitoring during operations. This range of cognitive readiness requires a serious investment in research covering a wide range of areas. This paper will present some of the focus of existing research and some of the paths for future research in this area as it applies to national security.

Critical Focus Areas for DOD S&T

Approximately three years ago the senior directors in the Office of the Deputy Under Secretary of Defense for Science and Technology selected five areas as especially critical in DOD's research program. These five research areas are the following: chemical and biological defense, hardened and deeply buried targets, information assurance, smart sensor web, and cognitive readiness. Today, these five areas seem to be obvious priorities, but three years ago that was not the case. These areas had existing research programs that were supported by the military service research programs and the defense agencies. The identification of these five areas by the Office of the Secretary of Defense gave them a corporate priority. Additional funds were provided to start new programs, to coordinate existing programs, and to support workshops to bring together new players who worked in various aspects of the areas.

The Department's focus on chemical and biological defense has been a clear priority for DOD over the last few years. The need for this research results from

proliferation of inexpensive weapons of both chemical and biological agents. DOD's research has four key areas of priority: detection of the agents, protection from the agents, decontamination of equipment and people after exposure, and an understanding of the dispersion of the agents from a modeling and simulation perspective.

Concern over hardened and deeply buried targets comes from the fact that underground facilities are often used to conceal missiles and weapons of mass destruction. DOD's research program includes priorities in overhead imagery to attempt to locate the targets, sensor research to determine what activities are being carried out underground, delivery systems to neutralize facilities if necessary, and computational modeling activities to understand the structures and activities within them.

Cyberterrorism is a real part of today's world. Attacks come from hackers, from terrorists, and from insiders. Dealing with information warfare is critical to assure that our information is protected and is not compromised. Research in information assurance involves designs of new firewalls, malicious code detectors, encryption techniques, and correlation technologies.

Smart sensor web is a concept that provides complete situation awareness to the individual soldier in the field. It is based on integrating information from areas such as realtime imagery, micro weather information, and moving targets. The research includes physical model understanding, dynamic data bases, microsensors, wireless communications, and the next-generation Internet.

Cognitive readiness addresses human optimization. The challenges to the human include sustained operations, environmental ambiguity, and information overload. Research programs address topics such as physiological monitoring, embedded training, learner-centric instruction, and augmented reality. Figure E.1 shows the wide range of areas covered by cognitive readiness.

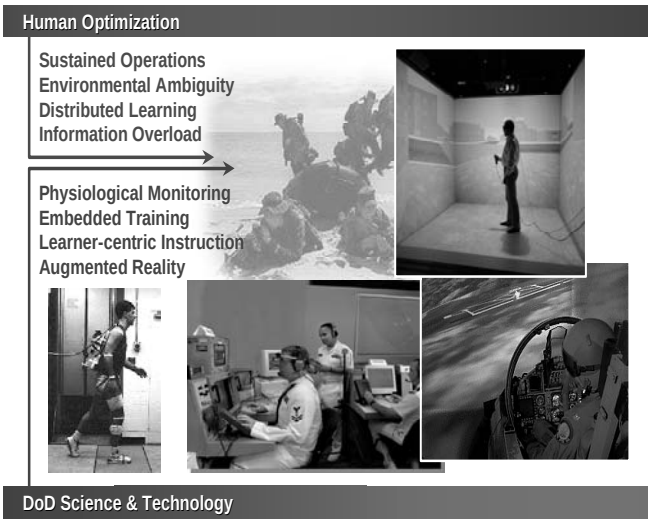

Figure E.1. Cognitive readiness research.

Cognitive Readiness Framework

The DOD has a multidisciplinary focus on the human dimension of joint warfighting capabilities. This cross-Service framework ensures that research addresses the following requirements:

- warfighters are mentally prepared for accomplishing their missions
- warfighters are performing at their optimum
- tools and techniques for preparing warfighters are the most effective and affordable
- tools and techniques that warfighters use are the most effective and affordable

The changing military environment compels a focus on cognitive readiness. Issues that affect this aspect of military readiness come from many directions. Soldiers have many different threats and changing missions that extend from peacekeeping to warfighting. Budget reduction brings personnel drawdowns in the military, and that brings demographic changes. In addition, military systems are becoming more complex, and soldiers need to handle new technologies. Figure E.2 illustrates the range of these interactions that soldiers must handle.

Four domains from science and technology research have been defined for cognitive readiness:

- *Sociology and personnel*. This domain deals with family, group, and culturally defined issues; selection and classification; and leadership.
- *Health and welfare*. This domain includes mental acuity, fatigue, physiological readiness, quality of life, and morale.

Figure E.2. Changing military environment.

- *Human systems integration*. This domain covers human-centered design, decision aids, and dynamic function allocation.
- *Education and training*. This domain includes using new technologies for teaching/learning and to develop specific tasks, skills, and/or procedures.

The following three examples demonstrate the wide range of research necessary to support cognitive readiness. *Augmented reality* involves bringing the information world to the soldier in real time. *Biomedical monitoring* combines sensors for measuring the physical readiness of soldiers to realtime monitoring to judge performance capability. *Survival technologies* present different areas of research to protect soldiers physically so that they are mentally and physically ready to perform their missions.

Example 1: Augmented Reality

Consider an urban environment. Soldiers need to know immediate answers to questions such as the following:

- How do I get to this building?
- What building is in front of me?
- Where is the main electric circuit in this building?
- What is the safest route to this building?
- Are there hidden tunnels under the streets?
- Street signs are missing – where am I?
- Have sniper locations been identified?

The area of augmented reality is an area in which technology is used to augment, or add, information for the soldier. For example, augmented reality could amplify natural vision by projecting information on a soldier's visor, or perhaps projecting it directly on the soldier's retina. This additional information added to the natural view could identify warnings for sniper locations and mines. Hidden infrastructure and utilities such as subways, service tunnels, and floor plans could be displayed. Virtual information such as simulated forces could be displayed to provide new training simulations. Figure E.3 gives an example of the type of information that would be very helpful if it were shown

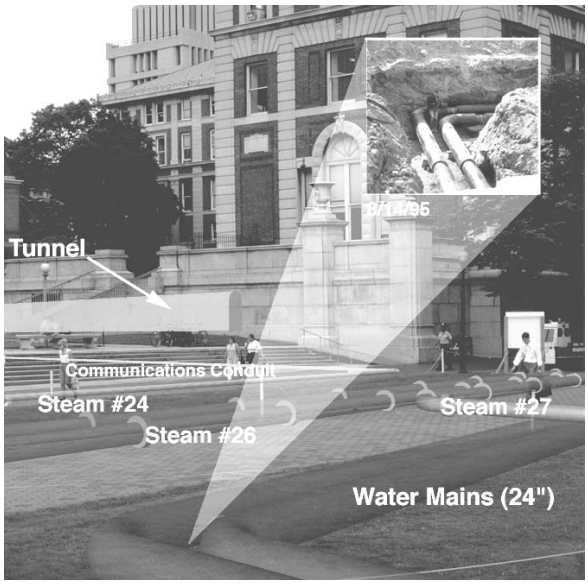

Figure E.3. Augmented reality.

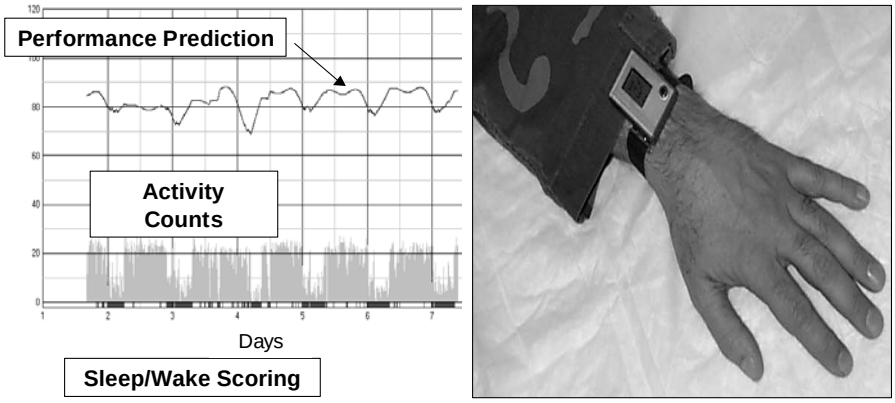

Figure E.4. Sustaining performance: managing sleep.

over an image to augment the information available to a soldier.

Example 2: Biomedical Status

Biomedical status monitoring is the medical equivalent of the Global Positioning System (GPS). It uses sensors for vital signs, electrolytes, stress hormones, neurotransmitter levels, and physical activity. In essence, it locates the soldier in physiological space as GPS does in geographic space.

The biomedical status monitoring program is integrated into several DOD programs, including Land Warrior, Warrior's Medic, and Warfighter Status Monitor. These programs allow dynamic operational planning with biomedical input that supports pacing of operations at sustainable tempo. It also allows commanders to anticipate and prevent casualties due to heat stress, dehydration, performance failures from sleep deprivation, and combat stress casualties. Not only can casualties be detected, but initial treatment can be guided.

Figure E.4 gives an example of a wrist monitor that predicts performance by monitoring sleep. Sleep is determined by the lack of motion of the wrist monitor. The graph in the figure predicts performance based on the amount of rest that the soldier has had.

Sensors can also help prevent casualties by monitoring soldiers in MOPP gear – the equipment worn to work in hazardous environments. The sensors can include core temperature (collected from a sensor that is swallowed by the soldier), skin temperature, heart rate, and activity rate. The combination of these sensors can be used to determine when a soldier needs to take a break in order to prevent possible injury or death.

Figure E.5 illustrates the hypothetical use of these biomedical status monitoring devices when they are combined with wireless communication systems. Individual soldier status can be monitored not only by soldiers working side by side, but also by central units that can be mobile or transmitted to satellite systems. Future sensors may also be embedded bionic chips.

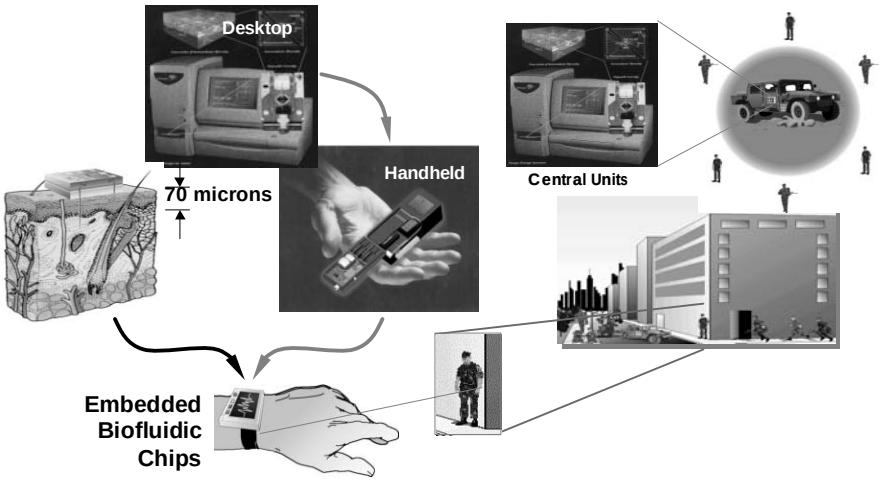

Figure E.5. Wrist-mounted remote biological assay.

Example 3: Survival Technologies

A number of new survival technologies are being developed to provide human protection in many different ways. Ballistics protection, shown in Figure E.6, is being studied using new high-performance fibers, composite materials, advanced ceramics, and metals. The analysis of new materials requires enhanced predictive modeling of the effects of ballistic weapons with these new materials. Another challenge is integrating the new materials into uniform systems.

Innovative research in chemical/biological protection for soldiers is investigating selectively permeable membranes that would provide an outer coating for uniforms. The coating would not allow aerosols or liquids to penetrate from outside the

Figure E.6. Ballistics protection.

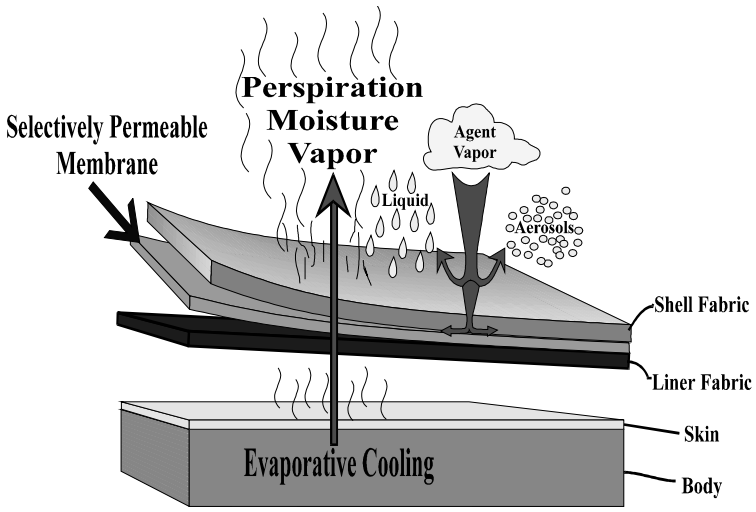

Figure E.7. Selectively permeable membranes for uniforms.

material. Additional research is being done in elastomeric protective materials and lightweight carbonless materials. Figure E.7 shows a diagram of some interactions between various layers of the material.

Directed-energy eye protection (protection from lasers) is a challenge because of the various frequencies of lasers. Some current systems are considering robust dielectric stacks on polycarbonate, enhanced-eye-centered holograms, operational dye technology, and nonlinear optical effects.

New materials are providing possibilities for multifunctional materials. Examples include aramid co-polymer chemistry and flame-retardant chemistry. Some of the possibilities for microencapsulation may provide phase-change materials — materials that change to match the environment of the soldier. This would provide a chameleon-like uniform.

Finally, systems integration will play an important part of combining many of the new capabilities such as microelectronics, improved lightweight sensors, and advanced materials. The work on high-resolution flat panel displays will provide wearable computer screens, and that will significantly reduce the weight of equipment that soldiers need to carry.

Conclusions

This article has briefly provided some of the reasons why cognitive readiness is such an important area to national security and identified some of the research that is being supported in this area. Successful research will require partnerships that bring together researchers from universities, government agencies, industry, and international coalitions. The benefits have far ranging possibilities that will address cognitive readiness not only of soldiers, but of general populations as well.

Acknowledgements

Significant contributions to this article were provided by Mr. Bart Kuhn from the Office of the Deputy Under Secretary of Defense for Science and Technology.

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DARPA'S PROGRAMS IN ENHANCING HUMAN PERFORMANCE

Michael Goldblatt, Defense Advanced Research Projects Agency

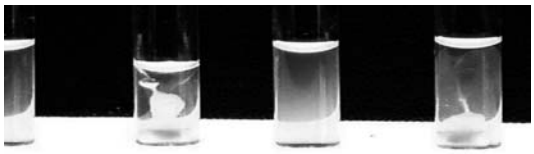
The Defense Advanced Research Projects Agency (DARPA) was established in 1958 as the first U.S. response to the Soviet launching of Sputnik. Since that time, DARPA's mission has been to assure that the United States maintains a lead in applying state-of-the-art technology for military capabilities and to prevent technological surprise from her adversaries.

With the infusion of technology into the modern theater of war, the human has become the weakest link, both physiologically and cognitively. Recognizing this vulnerability, DARPA has recently begun to explore augmenting human performance to increase the lethality and effectiveness of the warfighter by providing for super physiological and cognitive capabilities.

Metabolic Engineering

The Metabolic Engineering Program seeks to develop the technological basis for controlling metabolic demands on cells, tissues, and organisms. The initial phase of the program is focusing on the successful stabilization and recovery of cells and tissues from stress states representative of military operational conditions, with specific focus on blood and blood products (Figure E.8).

When successful, the application of this technology to combat casualties will result in greater salvage



Normal clot

Clot from Freeze-dried and reconstituted human platelets

Air dried and reconstituted embryonic stem cell

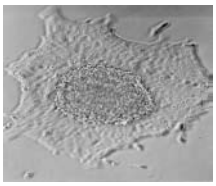


Figure E.8. Develop methods for controlled metabolism in cells, tissues, organs, and organisms needed by the U.S. military population.

of human life and limb from the battlefield, through the availability of cell-based therapy for hemorrhage, shock, and critical wounds. Additionally, stabilized cells and tissues will provide a stable substrate for prepositioning and large-scale manufacture of needed cellular and tissue products.

Exoskeletons for Human Performance Augmentation

The goal of the human performance augmentation effort is to increase the speed, strength, and endurance of soldiers in combat environments. The program will develop technologies, such as actively controlled exoskeletons, to enable soldiers to handle more firepower, wear more ballistic protection, and carry more ammunition and supplies, etc., in order to increase the lethality and survivability of ground forces in all combat environments (Figure E.9).

Two of the critical issues for exoskeletons are power for actuation and biomechanical control integration. The program is developing efficient, integrated power and actuation components to generate systems with duration that are operationally significant. Hence, researchers are exploring the use of chemical/hydrocarbon fuels (with very high energy density and specific energy) for energy conversion and mechanical actuation (as opposed to other energy storage media such as batteries or compressed air). An understanding of biomechanics, feedback, and control are also critical to building an integrated system that provides seamless compatibility with human kinetics, especially under battlefield stress.

Augmented Cognition

The DARPA Augmented Cognition program promises to develop technologies capable of extending the information management capacity of warfighters. This knowledge empowerment will be accomplished in part by exploiting the growth of computer and communication science and accelerating the production of novel concepts in human-computer integration (Figure E.10).

ISMS–Robot Supporting Human

Motion Capture System

Figure E.9. Incorporate and advance technologies to remove the burden of mass (120+ lbs.) and increase the soldier's strength, speed, endurance, and overall combat effectiveness.

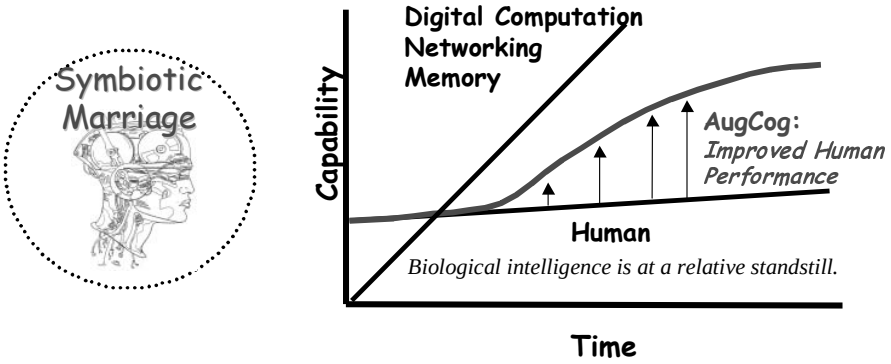


Figure E.10. Maintain a person's cognitive state at an optimal arousal level, then the person will have enhanced memory and the ability to perform optimally even under conditions of interruptions; this will improve and enhance the quality of military decisionmaking.

The mission of the Augmented Cognition program is develop and demonstrate quantifiable enhancements to human cognitive ability in diverse, stressful, operational environments. Specifically, this program will measure its success by its ability to enable a single individual to successfully accomplish the functions currently carried out by three or more individuals.

The program will explore the interaction of cognitive, perceptual, neurological, and digital domains to develop improved performance application concepts. Success will improve the way 21st century warriors interact with computer-based systems, advance systems design methodologies, and fundamentally reengineer military decisionmaking.

Continuous Assisted Performance (CAP)

The goal of this program is to discover new pharmacologic and training approaches that will lead to an extension in the individual warfighter's cognitive performance capability by at least 96 hours and potentially for more than 168 hours

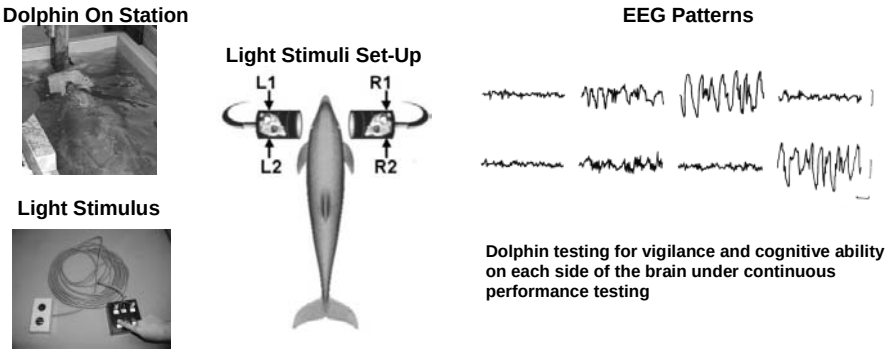


Figure E.11. Develop multifaceted approaches to prevent the degradation of cognitive performance caused by sleep deprivation in order to extend personnel "duty cycle."

without sleep. The capability to resist the mental and physiological effects of sleep deprivation will fundamentally change current military concepts of "operational tempo" and contemporary orders of battle for the military services.

The program will develop a number of different pharmacologic approaches using animal models (Fig. E.11) to prevent the effects of sleep deprivation over an extended period of time, nominally set at up to seven days. At the end of the program, we expect several candidate drugs that alone, or in combination, extend the performance envelope.

A minimum of four different approaches will be the core of the CAP program:

1. Prevent the fundamental changes in receptor systems of the information input circuits caused by sleep deprivation.
2. Discover the system that causes a reset of the network during sleep and develop a drug that activates this process in the absence of sleep.
3. Stimulate the normal neurogenesis process that is part of learning and memory, thereby increasing the reserve capacity of the memory circuits.
4. Determine if individuals resistant to sleep deprivation use a different strategy in solving problems and, if so, then develop a training approach that makes this possible for everyone.

Brain-Machine Interface

This program uses brain-machine interfaces to explore augmenting human

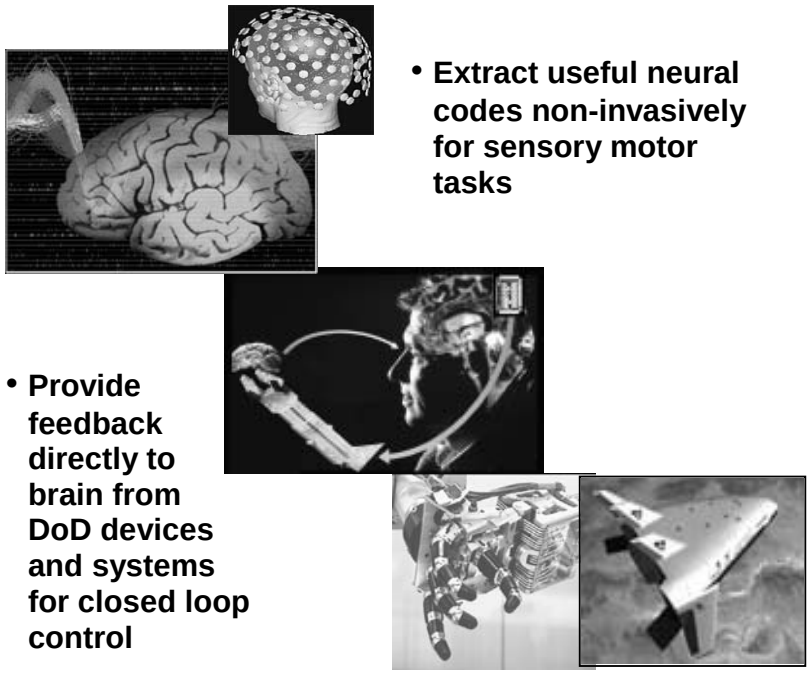


Figure E.12. Augment human performance by harnessing brain activity to command, control, actuate, and communicate with the world directly through brain integration and control of peripheral devices and systems.

performance by extracting neural codes for integrating and controlling peripheral devices and systems. The program attacks the technological challenges across many disciplines and will require assembly of interdisciplinary teams to achieve the ambitious goal of having humans interact with and control machines directly from brain activity.

Three of the significant challenges that the program will explore are as follows:

1. fundamental extraction of patterns of neuronal code as they relate to motor activity and the proprioceptive feedback necessary for executing motor commands
2. non-invasive access to the necessary brain activity (access a 500-micron square area where temporal spike train outputs can be measured)
3. design and fabrication of new machines (elasticity, compliance, force dynamics) that could be optimally controlled by the brain.

NBIC FOR HOMELAND DEFENSE: CHEMICAL / BIOLOGICAL / RADIOLOGICAL / EXPLOSIVE (CBRE) DETECTION/PROTECTION

James Murday, Naval Research Laboratory

The coupling of nanoscale sensors for chemical/biological/radiological/explosive protection (CBRE) with improvements in information technology and physiology can critically impact national security programs by providing sensitive, selective, and inexpensive sensor systems that can be deployed for advance security to the following kinds of locations:

- transportation modes (security protection for air, bus, train/subway, etc.)
- military (for protection of facilities and equipment)
- federal buildings (government offices, U.S. embassies, all other federal buildings)
- U.S. Customs (for border crossings, international travel, etc.)
- civilian businesses (in large and small cities)
- the environment (public water supplies, waste treatment plants, natural resource areas, reservoirs, etc.)
- schools (to prevent weapons, explosives such as pipe bombs, etc.)

Improvements in detection systems, coupled with new approaches to protection, promise potential impact that is vast and critical.

Role of Converging Technologies

Converging NBIC technologies will integrate the biology, chemistry, electronics, engineering, materials, and physics research communities to establish the interdisciplinary nanoscience knowledge and expertise needed to exploit nanofabrication and nanostructures in the development of the following:

- miniaturized, intelligent sensor systems with revolutionary CBRE performance

- new high-surface-area, templated adsorbents for personnel/collective protection systems
- nanofibers for effective clothing with minimal heat loading
- catalytic materials effective against agent while relatively benign to humans and environment
- mechanisms to disrupt biological agent viability

Nanotechnology will provide innovative new hardware. Information technology will provide the effective transformation of new data into information. Biotechnology will provide new insights into human physiology and prophylaxes. Together, these three technologies can lead to effective new protection systems against the CBRE weapons of mass destruction.

Transforming Strategy to Reach Vision

Short-Term (1-5 Year) Transition Opportunities

To be successful in the 1-5 year timeframe, opportunities must have already demonstrated proof-of-principle and have existing commercial interest. Specific examples include those shown in Table E.1.

Table E.1. Examples of Commercialized Nanotechnologies

Investigator	Institute	Technology	Company
Mirkin	Northwestern	nanoAu biological sensing	Nanosphere, Inc.
Lieber	Harvard	nanotube sensors	Nanosys
Snow	NRL	nanoAu chemical sensing	MicroSensor Systems
Klabunde	Kansas State	nanocluster agent catalysis	Nanoscale Materials
Thundat	ORNL	cantilever bio/chem sensing	Protiveris
Smalley	Rice	CNT for adsorbents	CTI
Doshi		polymer nanofibers	eSpin

SBIR and STTR funding can accelerate the transformation of the existing science discovery into technology ready for commercial attention.

Mid-term (5-10 Year) Transition Opportunities

Those areas where an investment in nanoscience holds the promise for paradigm-breaking approaches to detection/protection/neutralization with commercial product transition in the 5-10 year timeframe include the following:

Sensing

- transduction/actuation mechanisms for greater sensitivity/selectivity
- biotic/abiotic interfaces to marry semiconductors with *in vivo* biology
- environmental energy sources to minimize battery requirements

Protection

- high-surface-area materials with templated structure for selective adsorption

  - controlled porosity for separation
  - nanofibers for clothing with improved adsorption/neutralization of agent
- neutralization/decontamination
  - nanostructures to disrupt biological function
  - catalytic nanostructures
- Therapeutics
  - Encapsulated drugs for targeted release
  - MEMS "capsules" for controlled drug release

Long-Term (10-20 Year) Transition Opportunities

Investment in the science base long-term is believed to be important for ultimate integration of many components into a complex system (e.g., sensor suites) and for providing sufficient insights into a complex system (e.g., cell and spore physiology) to enable innovative technologies. Examples include the following:

- Laboratory on a chip — incorporation of multiple separation and detection technologies at sub-micron scales on a single chip in order to obtain inexpensive, rapid detection technology with low false positive/negative events
- Cell-based sensing — development of sensing technology that responds to unknown new threats by measuring the response of living systems that can mimic human biochemistry
- Nanoelectromechanical systems (NEMS) — extension of the MEMS technologies another three orders smaller in order to incorporate significantly more capability

Estimated Implications

Since the United States presently can dominate any military confrontation, it is highly likely that the nation will continue to suffer from terrorist actions such as the World Trade Center and the subsequent anthrax distribution. The application of convergent technologies to national defense has the potential for revolutionary new capability to counter the threats.

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FUTURE ROLES FOR SCIENCE AND TECHNOLOGY IN COUNTERTERRORISM

Tony Fainberg, Defense Threat Reduction Agency, Department of Defense

The natural reaction among scientists, engineers, and technical experts following the atrocities of September 11 was the fervent wish to apply their knowledge, abilities, and creativity in order to contribute to the defeat of current and future terrorist threats to the United States and its international friends and allies.

Indeed, there is ample opportunity for directing technical advances to this end. However, it should be emphasized that much can be accomplished nearly independently of technical innovations. Security procedures need to be improved in many venues. The most talked-about area today is aviation security; for example, the need to know who has access to airplanes at airports is pressing. Background checks to this end are now being instituted and, although enabled by advances in computer technologies of various sorts, can already be accomplished, given bureaucratic acquiescence. But although technical applications can enable these checks, the main barriers to doing so in the past have been cost, inconvenience, and concerns about intrusion on privacy. Another example is in the area of explosives detection. Excellent equipment for detecting explosives in baggage had been developed and manufactured as long ago as 1994. Since 1997, this equipment has been deployed and further developed, but it could be deployed in such a way as to cover the whole civil aviation system rather than just 10 percent of it. Under the current, new imperatives, these and a number of other matters can and will be solved through national resolve rather than advanced technology. Especially for the near-term, there is much that can be done to reduce our vulnerabilities (indeed, much is being done), without developing a lot that is new in the way of science and technology.

But, although science and technology are not the only answers to the diverse and menacing terrorist threat, they are part of the answer and will increasingly become so in the future. New integrated systems and approaches will be necessary both to increase the robustness of our society against bioattacks and to face newer threats, which themselves may be developed through the use of science and technology.

I will try to lay out some thoughts about where we might conceivably look for new tools to deal with threats that have occurred or that we can easily imagine occurring. My emphasis is on technologies that could begin to produce useful results in the mid-term (say, 2-3 years to 10 years), particularly those areas that are within the scope of this workshop's focus on the convergence of nanoscience/ nanotechnology, biotechnology/biomedicine, information technologies, and cognitive science.

Aviation Security[1]

One main problem in the area of aviation security that might be addressed by some of the NBIC technologies would be trying to find out (a) who the people are who have access to aircraft and (b) what their intentions are.

A second problem lies in the timely detection of chemical or biological agents, particularly in airports, and in what to do about the alarms, false and real. Chemical detectors are fairly good right now, although like everything else, they can be improved, especially regarding false alarms. One does need to program them to look for the particular agents of interest. The issues then are cost, where to deploy, and how to deal with false alarms. I will touch more on biosensors in the following section.

Infotech is the technical key to determining who the people are who have access to aircraft, and it also offers the first clues to their intentions. The people with access are those who work at airports, including screeners, and the passengers and crew. One problem is to distill information from various databases, most domestic, some international, to ferret out those individuals who are known or suspected to be threats. There will be resistance to sharing from those possessing the information on highly sensitive databases. At the minimum, a means must be found for providing only the essential information to the parties controlling access to the aircraft.

Biometrics, including facial recognition technologies, can in principle provide an additional identification tool, beyond the usual name, a minimal amount of personal data, and, perhaps, a picture. However, none of this is any use unless one has the individual of concern in one's database already. In the case of the 19 hijackers, from publicly available information, only three would have triggered any sort of alert. These were due to overstaying visas or having had minor run-ins with the law.

For those with access to aircraft, a serious background check needs to access databases that go back longer than a few months or even years: I would assert that it is necessary to track someone's credentials for eight years or more to get a clear enough picture of their potential for criminal conduct. And one constantly needs to verify that those granted access are actually the ones who have been approved for access. We don't want access given to someone who steals an ID, for example. Here, too, infotech and biometrics can only help with part (a substantial part, true) of the job. Procedural security changes are required to protect the civil aviation system adequately from the "insider" threat.

Regarding those who actually board a flight, it would be nice to know whether they have malevolent intentions that pose a risk to others. This is where some technological futurism might possibly be of use. Remote detection of heart rate, adrenaline on the skin, and perhaps other chemicals connected with the "fight or flight" reaction, is imaginable, and some efforts have been proceeding in these areas for years. Voice stress analysis is another possibility, although to my knowledge, there are no highly convincing data that this would provide a reliable trigger for the purposes considered here. And, in the neurological/cognitive realm, on an even

[1] For comparison with current work, the research and development plans for aviation security within the Federal Aviation Administration may be downloaded from the site, http://www.faa.gov/asd/red98.htm.

more futuristic note, would there be clues one could obtain from a remote (at a meter or two) electroencephalogram that would be useful?

I am somewhat skeptical of all of these possibilities, but the problem is serious enough, in my view, to justify some work in these areas. At the least, one could easily imagine useful by-products for public health and neurological research. Experimental data are needed to learn how reliable (if at all) such indicators would be in a civil aviation context. The obvious issues of effectiveness, false positives, and false negatives will be determinant: a simple demonstration of some vague effect is insufficient.

One needs to bear in mind that the consequences for an individual of triggering the system may not necessary be immediate incarceration for life. A trigger may simply indicate the need to examine carefully just what the individual has brought onto the plane. One might also want to correlate alarms from different individuals on the same flight. False positives, while they need to be controlled, can be tolerated at a moderately low level (say, less than a percent).

Information technologies could obviously be applied to the issue of monitoring or controlling a hijacked plane automatically or from the ground, as has been discussed openly in the press. All this is feasible with current processing, communications, and information technologies and appears to need little in further new research. Whether this approach (especially controlling flight) is a good idea or not, is another question. Pilots tend to think it is not.

Biodefenses

Sensors[2] (Refs)

It would be useful if highly sensitive, specific, broad-spectrum sensors, capable of detecting biological or chemical agents before they could threaten human life, were placed in many environments: transportation nodes, vehicles, public buildings, even homes. They should also be rapid (seconds to a few minutes at the most) and have manageable false alarm rates. What is manageable in this case is rather less than what is manageable in controlling airplane boarding. A false alarm rate of one per year per detector might be barely manageable in some contexts, unless one has the ability to run quick follow-up tests for verification. Even considering only public buildings, probably the most likely civilian target category for attack, the problem is still extremely challenging.

Biotechnology and nanotechnology (or, at least, microtechnology) converge here. There have been efforts in this area for years. I refer particularly to the "lab-on-a-chip" concept, which is being developed and used by national laboratories and private companies. For the purpose of protecting against terrorism (and serious work is going on in this area), one may envision arrays of perhaps up to 1000 by 1000 sites on a small chip, each one populated by a DNA sample from a particular

[2] Descriptions of government research and development work in chemical and biological detectors may be found in U.S. Department of Energy, *Chemical and Biological National Security Program, FY00 Annual Report* (Washington, DC: U.S. Department of Energy 2000) and U.S. Department of Defense, *Nuclear /Biological/ Chemical (NBC) Defense, Annual Report to Congress,* (Washington, DC: U.S. Department of Defense 2000).

pathogen. If one can sample well enough and devise a PCR process to be fast enough, one might imagine that highly specific detection would be possible. The rub is the time required: current prototypes that do DNA analysis typically require on the order of an hour to process a sample and have a rather small number of pathogens to which they are sensitive. The hope is to reduce this time to minutes or less.

If major improvements in biosensors are, indeed, possible within a few years, the applications in the public health arena are easy to imagine. If a national medical surveillance network is assembled, as some researchers envision (notable among them, Alan Zellicoff of Sandia) and many advocate, the use of an even broader pathogen-detection chip (if cheap enough) could have enormous benefits, both for monitoring and for individual treatment. The spin-offs would more than justify the expense incurred in the main counterterrorist thrust. This is an area I consider extremely fertile for more research and development, perhaps more than any other in the counterterrorist field, and one that needs even more attention than it is currently receiving.

Decontamination

Sensors would have obvious uses for decontamination after an attack. But what about decontaminating the air in buildings? There are current technologies that could be useful, as a matter of course, in buildings with high levels of circulation. Ultraviolet radiation, electron discharges, and nuclear radiation all come to mind as possibilities. As retrofits to current buildings, the cost would generally be prohibitive except for high-value targets. But if reasonable cost options were feasible, new buildings could incorporate such measures. This is an engineering issue and one that I suggest is worthy of some study.

Vaccines and Therapeutics

Vaccines and therapeutics are areas that have, of course, been pursued for a long time: centuries, in fact. Nowadays, the terrorist threat gives new impetus to these pursuits. Especially regarding vaccines, the lack of a strong market has made the large drug companies uninterested in working very hard in this area, and I assert that there is therefore a major role for the government.

A major new field is antiviral drugs, which is highly relevant to terrorism, since many putative agents, from smallpox to the hemorrhagic fevers, are viruses. To an outsider, this looks like a burgeoning subject of study, one poised on the cusp of serious breakthroughs. Major efforts need to be placed here. In this field of bioresearch, as well as many others, the stimulation of work for counterterrorist or defense ends will have many spin-offs for public health that are perhaps more valuable than the original purpose of the work.

Another approach is to look for methods to counter the chemistry and mechanics of infections, to look for commonalities in the way that different agents wreak havoc on multicellular organisms, and to counter the pathogen attack in a generic way. The Department of Energy, DARPA, and, indeed the whole field of microbiology actively work these areas of research. To an outside observer, again, the approach seems intriguing and promising. What I would suggest here is coordination of such work that particularly applies to microorganisms of interest as agents of bioattacks.

A totally different field that has received some attention lately, but probably not enough, is the area of edible vaccines.[3] Synthetically coding for receptor sites on the protein coats of pathogens, and then inserting these DNA strings into a plant genome has produced interesting early results. Workers at the Boyce-Thompson Plant Research Institute at Cornell, in collaboration with researchers at Baylor University, have found immune response in human subjects generated by eating the potatoes that result from such genetic manipulation. Since we have experienced such difficulties in producing a vaccine in large quantity just for anthrax, a totally different path might be in order. Side effects should be minimized by this technique. One could even imagine, eventually, a cocktail, a V-8, of tomatoes, bananas, or some other food, bred to protect against a variety of pathogens. The doses could be easily distributed and delivered, and, in remote or poor areas, would need a minimum of refrigeration and require no needles. Possibly, none of this will work out: maybe the required doses of food will just be too great or will have to be re-administered too often to be practical. But, it seems to me that this is interesting enough to investigate with more vigor than is currently the case.

Other Areas

Time and space severely limit what can be described in an extremely short paper. I will just touch upon other areas that appear to me to be important in combating terrorism. All would involve nanotechnologies and information sciences, falling under the NBIC rubric, since they would probably require advances in computing power to be most effective.

One can try to apply information technology and social sciences in an effort to discern patterns of behaviors in nasty organizations. If one were to focus on correlating a large volume of diverse data that include the characteristics, motivations, and actions, could one achieve any predictive value? Predicting a specific event at a specific time is clearly unlikely, but perhaps a result could be generalized cues that would enable intelligence services to look more closely at a given time at a given group. DARPA is pursuing such avenues, as are, no doubt, other branches of the government.[4] I would not call this cognition per se, but this type of effort does try to encompass, in part through behavioral sciences, how certain types of people might think in specific situations.

Finally, I would like to point to the issue of integrating architectures, applied to many counterterrorist areas. This, too, involves cognition and information science and technology. As a simple example, the security at an airport would greatly benefit from some integration of all the security activities that go on there, including alarms, alarm resolution, personnel assignments, equipment status, and so on.

On a much more complex level, the response to a major terrorist act, involving weapons of mass destruction, would benefit enormously from a generalized C4ISR (command, communications, control, computers, information, surveillance, and

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[3] http://www.sciam.com/2000/0900issue/0900langridge.html, also in *Scientific American*, Sept. 2000.

[4] http://schafercorp-ballston.com/wae/, accessed last on 27 December 2001, contains a description of a DARPA project entitled Wargaming the Asymmetric Environment.

reconnaissance) architecture. How does one put the response all together, among so many federal, state, and local agencies? How does urgent information get down to the street quickly and accurately? How is it shared rapidly among all those who urgently need to know? How does one communicate most effectively to inform the public and elicit the most productive public reaction to events? How can one best guide the decisions of high-level decisionmakers in responding effectively to the attack? How are their decisions most effectively implemented? True, we can always muddle through; we always have. But a comprehensive architecture for emergency response could make an enormous difference in how well the society will respond, and it could minimize casualties. And cognitive science and information technology together could greatly help in devising such architectures. Much talk and much work is proceeding in this area, especially in the past two months. My impression, however, is that thinking by newcomers to the counterterrorist field — who have the expertise in operations research, information technology, and cognitive sciences — would be highly productive.

NANOTECHNOLOGY AND THE DEPARTMENT OF DEFENSE

Clifford Lau, Office of the Deputy Under Secretary of Defense for Research

The Department of Defense (DOD) recognized the importance of nanotechnology well before the National Nanotechnology Initiative (NNI). DOD investment in nanoscience dated back to the early 1980s when the research sponsored by DOD began to approach the nanometer regime. Nanoscience and nanotechnology is one of six research areas identified by DOD as strategically important research areas. After careful evaluation and coordination with other federal agencies within the Interagency Working Group on Nanotechnology, the DOD investment was organized to focus on three nanotechnology areas of critical importance to DOD: Nanomaterials by Design, Nano-Electronics/Magnetics/Optoelectronics, and Nanobiodevices. DOD has traditionally provided leadership in nanotechnology research, particularly in the areas of nanoelectronics, chemistry, and materials. The research sponsored by DOD will provide the scientific foundation for developing the nanotechnology to enhance our warfighting capabilities.

DOD Impact

It is anticipated that nanotechnology would impact practically all arenas of warfighting in DOD, including command, control, communications, computers, intelligence, surveillance, and reconnaissance (C4ISR). In addition to providing much greater capability in computing power, sensors, and information processing, nanotechnology will also save more lives of our men and women in uniform by the development of lightweight protective armors for the soldiers. The value of nanotechnology to DOD includes, but is not limited to, the following:

a) *Chemical and biological warfare defense*. Nanotechnology will lead to the development of biochemical sensors to monitor the environment in the battlefield. Chemical and biological warfare agents must be detected at very low levels in real time. Nanotechnology will dramatically improve detection

sensitivity and selectivity, even to the point of responding to a few molecules of the biochemical agent. Nanostructures are showing the potential for decontamination and neutralization as well.

b) *Protective armor for the warrior*. Nanotechnology will lead to the development of extremely strong and lightweight materials to be used as bullet-stopping armors.

c) *Reduction in weight of warfighting equipment*. Nanotechnology will reduce the volume and weight of the warfighting equipment a soldier/marine must carry in the battlefield by further miniaturization of the sensor/information systems. Development in nanoelectronics and portable power sources based on nanotechnology will provide much-needed capability in information dominance in sensing, communication, situational awareness, decision support, and targeting.

d) *High-performance platforms and weapons*. By providing small structures with special properties that can be embedded into larger structures, nanotechnology will lead to warfighting platforms of greater-stealth, higher-strength, and lighter-weight structural materials. In addition to higher performance, new materials manufactured by nanotechnology will provide higher reliability and lower life-cycle cost. One example, already in fleet test by the Navy, utilizes nanostructured coatings to dramatically reduce friction and wear. In another example, nanocomposites where clay nanoparticles are embedded in polymer matrices have been shown to have greater fire resistance and can be used onboard ships.

e) *High-performance information technology (IT)*. Nanotechnology is expected to improve the performance of DOD IT systems by several orders of magnitude. Current electronics devices will reach a limit at 100 nm size in another five years. Continued advances in IT will require further advances in nanotechnology. Information dominance in network centric warfare and the digital battlefield is critical to DOD in winning the wars of the future.

f) *Energy and energetic materials*. The DOD has a unique requirement for energetic materials. Fast-release explosives and slow-release propellants must have high energy density while retaining stability. Nanoparticles and nano-energetic materials have shown greater power density than conventional explosives. Nanopowdered materials have also shown promise for improved efficiency in converting stored chemical energy into electricity for use in batteries and fuel cells.

g) *Uninhabited vehicles and miniature satellites*. Nanotechnology will lead to further miniaturization of the technology that goes into uninhabited vehicles and miniature satellites. The Uninhabited Air Vehicles (UAVs) will have greater range and endurance due to the lighter payload and smaller size. Uninhabited Combat Air Vehicles (UCAVs), will have greater aerial combat capabilities without the g-force limitations imposed on the pilot. Uninhabited Underwater Vehicles (UUVs) will be faster and more powerful due to miniaturization of the navigation and guidance electronics.

DOD Programs

Because of the large potential for payoffs in enhancing warfighting capabilities, nanotechnology continues to be one of the top priority research programs within the Department of Defense. In the Office of the Secretary of Defense, the DURINT (Defense University Research Initiative on Nanotechnology) will continue to be funded out of the University Research Initiative (URI) program. All three services and DARPA have substantial investments in nanotechnology 6.1 basic research. New 6.2 applied research programs are being planned to transition the research results to develop the nanotechnology for DOD.

ADVANCED MILITARY EDUCATION AND TRAINING

James Murday, Naval Research Laboratory

The U.S. military annually inducts 200 thousand new people, 8 percent of its person power. Further, the anticipated personnel attrition during warfare requires extensive cross-training. With public pressure to reduce casualties, there is increasing utilization of high technology by the military. Warfighters must be trained in its use, recognizing that the education level of the average warfighter is high school. These circumstances present the military with an education and training challenge that is exacerbated by the fact that personnel are frequently in remote locations — onboard ship or at overseas bases — remote from traditional education resources. The entire K-12 education in the United States has similar problems, so any program that successfully addresses military training needs will certainly provide tools to enhance K-12 education as well.

The convergence of nano-, bio-, info- and cognitive technologies will enable the development of a highly effective teacher's aide — an inexpensive (~$100) virtual learning center that customizes its learning modes (audio, visual, and tactile) to individuals and immerses them into a custom environment best suited for their rapid acquisition of knowledge.

Role of Converging Technologies

Nano. Nanotechnology holds the promise for relatively inexpensive, high-performance teaching aides. One can envision a virtual-reality teaching environment that is tailored to the individual's learning modes, utilizes contexts stimulating to that individual, and reduces any embarrassment over mistakes. The information exchange with the computer can be fully interactive — speech, vision, and motion. Nanodevices will be essential to store the variety of necessary information or imagery and to process that information in the millisecond timeframes necessary for realtime interaction.

Bio. Biotechnology will be important to provide feedback on the individual's state of acuity and retention.

Info. Information technology must develop the software to enable far more rapid information processing and display. Since military training must include teaming relationships, the software must ultimately accommodate interaction among multiple parties. Innovations are also needed to enable augmented-reality manuals whereby

an individual might have realtime heads-up display of information that cues repair and maintenance actions.

Cogno. Effective learning must start with an understanding of the cognitive process. People have different learning modes — oral, visual, tactile. They respond to different motivators — individual versus group — and different contexts — sports for the male, social for the female, to use two stereotypes. Human memory and decision processes depend on biochemical processes; better understanding of those processes may lead to heightened states of acuity and retention.

Transforming Strategy to Reach the Vision

Under its Training and Doctrine Command (TRADOC, http://www-tradoc.army.mil/), the U.S. Army has a Training Directorate that endeavors to introduce more effective training and education methods. A collaborative program between the National Nanotechnology Initiative, the National Information Technology Initiative, NSF (science and math), the Department of Education (K-12 teaching), and TRADOC might lead to the most rapid progress toward this goal. The entertainment industry must also be included, since it has been a driver behind much of the recent technological progress

Estimated Implications

This opportunity has benefit for education and training of students at all age levels, not just the military. Further, all technology benefits from larger markets to lower the unit cost. A low-cost instruction aide as described above, especially in mathematics and science, could bypass the problem of preparing adequately knowledgeable K-12 teachers. Success at this project could revolutionize the nation's approach to education.

VISIONARY PROJECTS

HIGH-PERFORMANCE WARFIGHTER

James Murday, Naval Research Laboratory

If one were to look for situations where the confluence of nano, bio, info and cogno technologies would make a critical difference, the military warfighter would certainly be seriously considered a leading example. The warfighter is subjected to periods of intense stress where life or death decisions (cogno) must be made with incomplete information (info) available, where the physiology of fatigue and pain cloud reason (bio), and where supplemental technology (nano) must compete with the 120 pounds of equipment weight s/he must carry.

The confluence of the NBIC technologies will provide the future U.S. warfighter with the capability to dramatically out-fight any adversary, thereby imposing inhibitions to using warfare with the United States as a means to exert power and reducing the risk of U.S. casualties if war does occur.

Role of Converging Technologies

Nanotechnology holds the promise to provide much greater information, connectivity, and risk reduction to the warfighter. The continued miniaturization of electronic devices will provide 100 times more memory (a terabit of information in a cm^2). Processing speeds will increase to terahertz rates. Displays will be flexible and paper thin, if not replaced by direct write of information on the retina. High-bandwidth communication will be netted. Prolific unattended sensors and uninhabited, automated surveillance vehicles under personal control will provide high data streams on local situations. The marriage of semiconductors and biology will provide physiological monitors for alertness, chemical/biological agent threat, and casualty assessment. Nanofibers and nanoporous adsorbents will protect against CB threats while minimizing heat burdens and providing chameleon-like color adaptation for camouflage. The small size of the nanodevices will limit the volume, weight, and power burdens.

Presuming nanotechnology delivers the hardware, advances must be made to create information out of the manifold data streams. The soldier must stay alert to the environment, heads-up or retinal displays are essential, as well as the traditional flat, flexible (paper-like) media. Voice dialogue with the computer is essential to keep hands free for other functions. GPS-derived location, high-precision local maps (cm^2 voxels — potentially three-dimensional representations that include information about building structures, underground tunnels, and the like); language translators (for interrogation of the local citizenry); automated weapons that track target location and control the precise moment to fire: all of these capabilities will require new software.

Biotechnology promises considerable advances in monitoring and controlling the physiological condition of a warfighter. New innovations are likely to include sensitive, selective transduction of biological events into signals compatible with electronic devices; new approaches to the neutralization of biological and chemical agents without aggressively attacking other constituents in the local environment; and possible harnessing of body chemistry as a source of local power.

The nano-, info-, biotechnology items above are aids toward more effective learning and decision making. Rapid, effective cognition is critically dependent on body physiology, and on the manner information is organized and delivered (audio, visual, tactile) (Figure E.13).

Transforming Strategy to Reach the Vision

Nanoscale science, engineering, and technology will provide the understanding critical to rapid progress in the development of new, higher-performance, information technology nanodevices, of high performance materials, and of sensors/activators for biological systems. In a simplified, but useful, perspective, nanoscience will underpin the information technology and biotechnology components of a warfighter system program. The National Nanotechnology Initiative (NNI) will provide a broad-based program in nanoscience; it remains a challenge to couple that program most effectively with information technology and biotechnology.

Information Technology (ITI) is also a U.S. national initiative. The coordinating offices for both the NNI and ITI programs have been collocated in order to

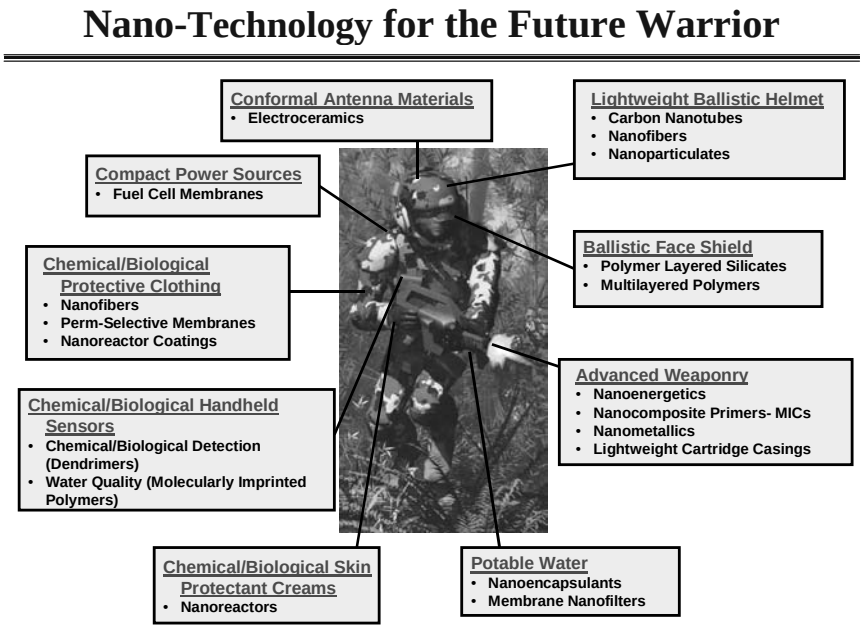

Figure E.13. Soldier system of the future (courtesy Dr. Andrzej W. Miziolek, U.S. Army Research Laboratory, AMSRL-WM-BD, Aberdeen Proving Ground, MD).

encourage close collaboration. The Information Technology Initiative identifies areas where advances in device capability would be most effective and works to advance modeling and simulation (high-performance computing) so that theoretical contributions to nanoscience will be an equal partner with the experimental efforts. The Nanotechnology Initiative must accelerate progress in those areas where new, cost-effective technology will lead to the most significant impact on information systems.

Biotechnology is effectively a third U.S. national imitative if one includes the NIH budget for health and medicine. A principal challenge here is acceleration of chemical, physical, materials, and engineering contributions to biotechnology. Biology must also better identify the biochemical basis for alertness, acuity, and memory retention.

The large investments already present in nano-, info- and biotechnology should be coordinated and coupled with efforts in cognition. DARPA, NASA, NIH, and NSF already have major programs that seek to integrate nano-, bio- and info- research. Within the DOD, the Army and Marines have the lead efforts in technologies to impact the individual warfighter. The Army is presently competing a University-Affiliated Research Center (UARC) on

Figure E.14. Wearable device for non-drug treatments.

the topic, "Institute for Soldier Nanotechnologies," that potentially can integrate the essential components of this opportunity.

Estimated Implications

Technology has led to dramatic improvements in fighting capability, but not for the individual soldier or marine. While air and sea power certainly have a major role in attacking any opponent, in any major conflict, soldiers and marines will be engaged in ground combat. Utilizing the convergent NBIC technologies, we have the opportunity to improve significantly the ability to control the local situation at minimal risk of personal casualty.

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NON-DRUG TREATMENTS FOR ENHANCEMENT OF HUMAN PERFORMANCE

Robert Asher, Sandia National Laboratories

Human performance enhancement may require modifications to the biochemical aspects of the human. Maintained alertness, enhanced physical and psychological performance, and enhanced survivability rates in serious operations all require modifications to the biochemical aspect of the human. DARPA is in the process of developing drugs to enhance performance when a person has been sleep-deprived. Drug companies spend an average of $800 million to develop new drugs that may have negative side effects. An alternative is to develop non-drug approaches to human performance enhancement. As an example, it is common medical practice to immerse a person in a hot bath preceding heart operations to build up stress proteins that will give greater survivability when s/he receives blood products.

Consider the use of externally applied, non-dangerous electromagnetic fields to increase the rate of production of body biochemicals that enhance human performance. DARPA has a proposal to increase the rate of stress protein production before a soldier goes into combat. The intent is to increase the survivability rate when the soldier is wounded and needs to receive blood products. Beyond that, one can envision increasing the rate of production of ATP, which will yield higher energy levels by natural means, will help ion pumping to aid in nerve recovery and contraction of muscles, and will speed recovery from combat stress. What other changes can be engineered by a specifically shaped electromagnetic pulse that might enhance human performance without pharmaceuticals? This investigation may spawn a new industry in which the human is enhanced by externally applied electromagnetic pulses so shaped as to enhance specific biochemical changes within the body without drugs or in combination with drugs, with fewer side effects. For instance, nanoparticles might be formulated to release drug dosages only when

irradiated with electromagnetic pulses focused at certain sites, allowing treatments to specific areas without the whole body being affected by the drug therapy.

Role of Converging Technologies

All of the NBIC technologies have a role in the goals of non-drug enhancement of human performance:

Nano. Develop and understand the nano aspects of the use of electromagnetic field interactions with cellular structures. Develop and understand how treatments may be developed by nano particle interactions only at specific sites where the electromagnetic fields are focused. Investigate whether electromagnetics can be used as a power source to conduct mechanical actions at the sites.

Bio. Develop a detailed understanding of the effects of electromagnetics on cells and neuronal networks, including the full range of scales, from micro effects on proteins to macro effects on neuronal networks.

Info. Develop methods to shape optimal electromagnetic pulses to carry messages to the cells and neurons.

Cogno. Understand how electromagnetics can be used to enhance cognitive performance as well as physiological performance.

Transforming Strategy to Reach Vision

The strategies to achieve these goals are as follows:

- Develop a program that will explore the use of electromagnetics for enhancement of human performance. This program will be multidisciplinary in orientation, utilizing
  - electromagnetics as the actuation mechanism for the treatments
  - biotechnology in the understanding of cellular interaction with the electromagnetic fields
  - nanotechnology to help engineer solutions that may include specific site treatments released by a focused electromagnetic field
  - information technology in that the pulses need to be so shaped as to cause desired interconnected cell electromagnetic responses of cognition by external fields
- Fund work towards the goal of understanding in detail the effects of electromagnetics on cellular systems and on cognition.
- Consider cellular electrochemical and structural changes and actions imposed by electromagnetics.
- Fund work towards electromagnetic and biochemical dynamical modeling of cellular systems in order to both understand electromagnetic and biochemical aspects, as well as to optimize the shape of electromagnetic pulses to impose desired cell changes without inducing side effects.
- Fund experimental basic work in understanding the effects of electromagnetics on cells.

Estimated Implications

The impact on society of such a program can be great, as this might yield treatments to enhance human performance without the use of drugs and provide new exciting treatments for ailments that require site-specific treatments. A new industry can be born from this work. It may also lead to treatments that will enhance human cognition.

BRAIN-MACHINE INTERFACE

Robert Asher, Sandia National Laboratories

Increasingly, the human is being asked to take in multisensory inputs, to make near-instantaneous decisions on these inputs, and to apply control forces to multitask and control machines of various sorts. The multitasking, multisensor environment stresses the human, yet, more and more s/he being asked to operate in such an environment. As an example, the visionary project on uninhabited combat vehicles discusses an increased workload in piloting combat vehicles. DARPA has a brain-machine interface program about to start. This program has as its goal human ability to control complex entities by sending control actions without the delay for muscle activation. The major application for this program is control of aircraft. The intent is to take brain signals and use them in a control strategy and then to impart feedback signals back into the brain.

The DARPA program could be extended to include a broader range of potential impact by including the possibility of other applications: learning and training, automobile control, air traffic control, decision-making, remote sensing of stress, and entertainment. Learning and training might be implemented as information coded into brain signals and then input into the person. Air traffic control in increasingly busy skies can use such capability: the controller has multiple inputs from multiple aircraft. These can be input into his brain in a 3-D aspect and an alertness signal used to "wake him up" when his attention drifts beyond acceptable limits. Not only intellectual data might be passed from one person to another without speaking, but also emotional and volitional information. Decision-making may become more precise as emotional, fatigue, and other cognitive states can be appraised prior to making a critical decision.

The potential impact on automobile safety is great. The driver can have quicker control of his automobile (Figure E.15), allowing for safer driving while reducing the car-to-car spacing on congested highways. This would help alleviate highway congestion and the need for more highways. Furthermore, it would allow for safer driving as driver attention can be measured and the driver "alerted" or told in some manner to pay attention to his or her driving when attention wanders beyond safe margins. It can allow for detection of driver impairment so that the vehicle may be made either not to start or to call emergency.

Direct connection into the brain could yield a revolution in entertainment, as people may be "immersed," MATRIX-style, into the midst of a movie or educational show. Can you imagine the impact of being immersed in a fully 3-D audio-visual simulation of the battle of Gettysburg?

Figure E.15. Hands-off control of an automobile through a device for reading and implanting brain waves.

Role of Converging Technologies

Nano. The brain-machine interface effort will require nanotechnologies in order to make the required experimental measurements and to implement the devices for both receiving brain electromagnetic signals and transmitting signals back into the brain.

Bio. This is a highly biological, neuroscience effort, which requires detailed understanding and measurements of the brain's electromagnetic activity. It requires a significant measurement protocol.

Cogno. This effort by its very nature will directly affect the cognitive aspects of the individual by externally applied electromagnetic fields by implanting information for the individual. Thus, this effort can lead to increased learning and other cognitive results.

Transforming Strategy to Reach the Vision

To achieve these goals, enter a partnership with DARPA to fund additional technologies and applications that would enhance the brain-machine interface effort. Work should be focused on the goals of using the technologies for cognitional aspects, understanding memory, and learning brain function to be able to design devices to increase their capabilities.

Estimated Implications

This effort would yield a technological revolution, in applications from computers to entertainment. It would give the United States a global competitive advantage while yielding solutions to specific domestic problems such as air traffic control and highway safety in increasingly crowded environments. It will revolutionize education. This effort will yield devices that may be applied to a number of activities and be sufficiently small as to be wearable in a car or at home.

NANO-BIO-INFO-COGNO AS ENABLING TECHNOLOGY FOR UNINHABITED COMBAT VEHICLES

Clifford Lau, Office of the Deputy Under Secretary of Defense for Research

It is envisioned that in 20-30 years, when the research and development are successfully completed, nano-bio-info-cogno (NBIC) technology will enable us to replace the fighter pilot, either autonomously or with the pilot-in-the-loop, in many dangerous warfighting missions. The uninhabited air vehicle will have an artificial "brain" that can emulate a skillful fighter pilot in the performance of its missions. Tasks such as take-off, navigation, situation awareness, target identification, and safe return landing will be done autonomously, with the possible exception of person-in-the-loop for strategic and firing decisions. Removing the pilot will result in a more combat-agile aircraft with less weight and no g-force constraints, as well as reduce the risk of pilot injury or death. The fighter airplane will likely derive the greatest operational advantages, but similar benefits will accrue to uninhabited tanks, submarines, and other military platforms.

Role of Converging Technologies

The convergent NBIC technologies, although at the early stage of basic research, are anticipated to have an impact on practically all arenas of warfighting and peacekeeping and thus are vitally important to national security. For instance, today's fighter airplanes are loaded with sensors, avionics, and weapon systems. The complexity of these systems and the information they provide place tremendous workload on the pilot. The pilot must fly the fighter airplane in hostile environment, watch the cockpit displays, be aware of the situation, process the sensor information, avoid anti-air missiles, identify and destroy the targets, and return safely. No wonder there is information overload on the pilot, in spite of the many decision aid systems. Furthermore, fighter pilots are highly valued and trained warriors, and the country cannot afford to lose them from anti-air fire. The need for autonomous or semi-autonomous air vehicles to accomplish surveillance and strike missions is clear (Figure E.16).

Nano. Nanotechnology will continue to the current trend in miniaturization of

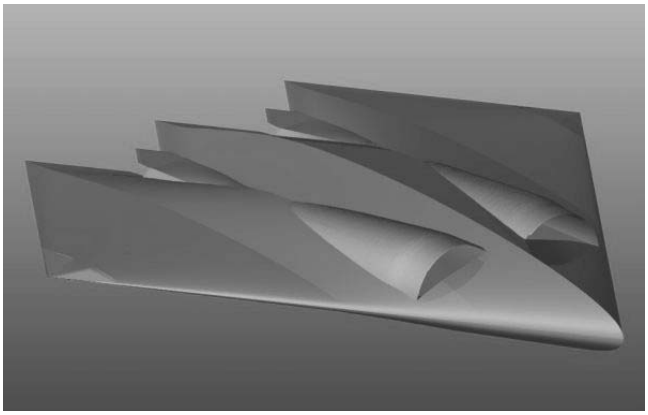

Figure E.16. Uninhabited combat air vehicle (UCAV).

sensors, electronics, information processors, and computers. Miniaturization will reduce the weight, size, and power of the on-board systems in the air vehicle and will increase information processing power.

Bio. Brain research will help us to understand how pilots process the massive amount of information coming from the sensors and intelligence. That understanding will allow us to design an artificial "brain" to process the information and to control the air vehicle autonomously.

Info. Research in information technology will enable us to design specialized systems that do not require writing millions of lines of code, such as the adaptive learning strategy used by the brain. Storage and retrieval of massive amounts of data and information fusion to allow the system to make decisions will also be an important aspect of this research.

Cogno. Understanding the principles behind cognition is extremely important in the design of an autonomous system with the capabilities of target recognition and situation awareness. For autonomous air vehicles, it is particularly important to recognize the intent of encounters with friendly or unfriendly aircraft in its vicinity.

Transforming Strategy to Reach Vision

The DOD presently has a number of projects working toward uninhabited combat aircraft. The challenges to meet this goal are considerable. An NBIC program centered at universities would provide both the scientific discovery and the trained students that will be necessary for those projects to succeed quickly. In order to achieve the vision stated above, it is necessary to plan a coordinated and long-term research program considering the above strategies on how to get there. It is important to integrate the current research efforts on nanotechnology with the other research areas to form a multidisciplinary research program. A university-based basic research program addressing the needed science must be interactive with the DOD programs addressing system design and manufacture.

Estimated Implications

Removal of the pilot from assault and fighter aircraft will reduce the risk of injury or death to highly trained warfighters. American public opinion makes this a clear priority. In addition, the lighter weight (no pilot, oxygen system, ejection system, man-rated armor, canopy, etc.) and absence of human g-force constraints will make the aircraft either more maneuverable or capable of more extended missions.

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DATA LINKAGE AND THREAT ANTICIPATION TOOLS

Tony Fainberg, Defense Threat Reduction Agency

The United States will be subject to asymmetric military threats from lesser powers. On 11 September 2001, this observation moved from the theoretical to the real. To deal adequately with the future, the United States must develop an intelligence system to anticipate threats from adversary states or sub-state actors.

Role of Converging Technologies

The suggested approach is to use the power of *information technology* to assemble, filter, and analyze data about the adversary. First, it will be necessary to acquire a large volume of data regarding each potential enemy organization. Data linkage among many databases would be needed, including some from open source material and others from intelligence sources. The data would include the group's characteristics, its people, funds, and the movement of each, the motivations of the people, relevant current events, significant dates, and some way of encoding the cultural perspectives of the organization. In addition to information technology, the approach also requires *nanotechnology*, due to the large amount of data that need to be handled and analyzed. Further, some sociological analysis (for the group) and psychological profiling would be required, as well as country and culture experts. This requires broad social science input. Understanding how the adversary analyzes and makes decisions involves modeling his *cognition* processes. An automated translation capability would be helpful in the data mining, since frequently there may not be enough analysts familiar with the necessary languages to keep up with the data input.

Transforming Strategy to Reach Vision

DARPA's Information Technology Office is pursuing similar methodologies, as have, no doubt, other branches of the government. It is possible that increased computing power, better application of the social sciences, plus more sophisticated integration of the information and modern decision algorithms might produce significantly better predictive tools. The National Science Foundation is in an excellent position to sponsor research in this area, as well as to coordinate similar programs of other agencies through interagency workshops.

Estimated Implications

The resulting decision tool or decision aid would probably not be able to predict a specific event at a specific time; however, it could possibly function to cue intelligence services to look more closely at the adversary when it gives an alarm and might also be useful for cueing heightened security alerts.

F. UNIFYING SCIENCE AND EDUCATION

THEME F SUMMARY

Panel: D.L. Akins, Y. Bar-Yam, J.G. Batterson, A.H. Cohen, M.E. Gorman, M. Heller, J. Klein-Seetharaman, A.T. Pope, M.C. Roco, R. Reddy, W. Tolles, R.S. Williams, D. Zolandz

The fifth and final NBIC theme explores the transformations of science and scientific education that will enable and be enhanced by technological convergence. The panel especially focused on the ways that education can transform science and unifying science (based on the unity of nature and using cause-and-effect explanation) can transform education, for the vast improvement of both. As a number of reports from the National Research Council (NRC 1996-2000) and comparable organizations attest, the future of society depends on continued scientific progress, which in turn depends upon science education. Converging scientific principles and technologies will raise the importance of this issue to a higher level.

Four factors demand significant changes in the science education received by students at all levels:

1. Many poorly understood social factors work against science in the educational system, and ways must be found to counter these anti-science forces using new S&T trends (NSF 2000).
2. Rapid progress in cognitive, biological, information, and nanoscale sciences offers new insights about how people learn that can guide effective reforms in curriculum, evaluation, and organizational structuring.
3. New education techniques and tools will be made available by converging technologies, and we need to prepare to take advantage of them.
4. Few mid-career professional scientists have the practical opportunity to redirect their careers to any significant extent, so unification of the sciences must largely begin in school.

Currently, scientific and engineering education is highly fragmentary, each part constrained by the boundaries of one particular discipline. In the future, the knowledge taught will be based on unifying concepts offered by nano, bio, info, and cognitive sciences throughout the educational establishment. Natural, engineering, social, and humanity sciences will converge. The corresponding basic concepts of unifying science will be introduced at the beginning of the teaching process in K-12, undergraduate, and graduate education. New tools will be developed by convergent technologies to provide high-quality, anywhere-anytime educational opportunities. NBIC science and engineering education will be made available to the majority of students and as continuing education to all interested adults.

No single discipline can describe or support the converging technologies by itself. Different disciplines may play a leading role in different applications. Interfaces are beginning to develop among the four NBIC domains, linking them in pairs, trios, and as a full quartet, in parallel with in-depth development within each

field. The optimal process will not develop naturally: a systematic program must be created to encourage it.

Within academia, significant challenges must be overcome. Many teachers lack sufficient depth in their knowledge of mathematics and science, and not enough of the best students are attracted to science and technology. Also, qualified personnel who do understand science and technology generally get better-paying jobs outside the field of teaching.

What Can NBIC Do for Education?

The unification of the sciences is gaining momentum and will provide a knowledge base for education. The concepts on fundamental building blocks of matter employed in nanoscience can be applied in different disciplines, thus providing a multidisciplinary opportunity to introduce breadth while advancing depth. This creates the opportunity for integration across learning — moving from reductionism to integration. It also introduces the challenge of creating a common language for talking about the big picture.

Technologies that arise from the NBIC convergence will provide new tools and modalities for teaching. Some of these will be sensory, including visual, auditory, and tactile. Others will take advantage of better understanding of how the brain works. Still others will be logistic and include delivery of teaching and educational resources any time and anywhere. For advanced levels of scientific training, this will create opportunities at new research frontiers.

Across all levels, there will be opportunities to involve groups of people who have tended previously to be excluded from high-quality science education. We have a responsibility to achieve substantial inclusion and outreach, especially across race and gender. The entire 21st century workforce will be involved in the convergent technologies revolution. NBIC-related applications will be an excellent way to promote systemic, problem-based learning from the earliest educational levels.

What Can Education Do for NBIC?

Universities epitomize the ideal of uniting the intellectual heritage of mankind, so they are a relatively hospitable environment for scientific and technological convergence. Other kinds of educational institutions can also play crucial roles in bringing the scientific and technical disciplines together. In the economy, certain markets become trading zones where a great diversity of products, services, and institutions converge. Scientific trading zones will have to be created, perhaps anchored in university-based research centers or in joint academic-industrial partnerships, that will allow students and scientists to develop the necessary communication skills for trading ideas across disciplines.

The educational system can provide a stimulus for drawing recruits into the NBIC community. Classrooms can become a proving ground for exploring new technologies designed to facilitate learning and communication. Similarly, the educational system can be a developmental laboratory for testing useful technological directions in NBIC.

Many new educational approaches will have to be tried in order to see which are most effective in achieving technological convergence. For example, universities may offer retraining for scientists who already have doctorates and may already

have extensive experience in industry or research laboratories. Perhaps young scientists will engage in post-doctoral work in a second field. NBIC will benefit from changes in life-long learning at all levels, including in both white-collar and blue-collar occupations. NBIC concepts must be adopted early, in advance of technological developments that would require a qualified workforce.

NBIC is likely to be both creative and destructive at all levels of the scientific, economic, and social establishment, for example, creating new industries and companies, with the inescapable result that some older ones will decline or even become extinct. Thus, it will be important to educate society about the potential unintended consequences of technological innovation. Maximizing the societal benefits of a new technology is essential for it to enjoy full public support (Roco and Bainbridge 2001).

NBIC Education for the Twenty-First Century

To enhance human performance most successfully, science and engineering education will have to evolve and, in some respects, radically reinvent itself. The knowledge taught will be based on concepts offered by nano, bio, info, and cognitive sciences, and these concepts will be introduced at the beginning of the K-12 teaching process. High-quality science education will be made available to the majority of students.

Special efforts must be made to stimulate communication between disciplines and develop in scientists the communication skills for doing so, so that conversations between them can be made focused and productive. Achievement of good interdisciplinary communication will synergistically enhance the knowledge and progress of all disciplines. Since mathematical tools represent a common language among and between disciplines, mathematics should be taught in greater depth and be a common focus among most scientific disciplines. At the same time, mathematics textbooks must use problems from science and engineering as examples.

Concerted efforts must be supported to write cross-disciplinary educational materials, using a variety of media at the university level that help with the language problems across traditional fields. A positive, inclusive social environment must be promoted that encourages creative growth of converging technologies. Improved pedagogy and accessibility are fundamental ingredients for the realization of converging technologies, incorporating the cultural differences that exist between students and between different technical fields.

At the college and graduate school levels, we may need a new program for multidisciplinary fellowships that would make it possible for students to move among professors and disciplines related to NBIC. A fellowship might travel with a student from one department or school to another and temporarily into a research integration or industry unit. Students might be allowed to define their own cross-disciplinary proposals, then funding would be provided directly to them rather than to an institution or mentor.

Depth in graduate studies is necessary and should not be compromised. However, if specific disciplines deliberately associate themselves with neighboring disciplines that use similar tools and models, breadth and a holistic perspective will come more easily to all.

Creating new educational curricula and methodologies will require problem-driven, system-oriented research and development. Cognitive scientists can analyze learning styles using NBIC and provide appropriate assistance. Better education is needed for teachers, including sufficiently funded research experiences and credit for in-service experiences in industry and research laboratories.

NBIC concepts should be introduced as early as possible. For example, basic concepts and problems of nanoscience could be taught in elementary schools. NBIC terms and concepts could be placed into childhood educational reading materials starting from the earliest levels. Virtual reality environments and websites could offer many kinds of exciting instructional materials. Practical demonstration kits could facilitate interactive learning. Research scientists could frequently visit schools to offer demonstrations and serve as role models.

NBIC courses and modules can be integrated to some extent into existing curricula and school settings, but novel alternatives will also have to be explored. Every way of making science and technology more interesting for young people would be helpful, such as using games to teach math and logic. To achieve these goals, it will be essential for educators, including members of school boards, curriculum development committees, and designers of standardized tests, to identify and encourage champions in K-12 schools. National standards for educational achievement will be indispensable tools to address the most challenging and promising NBIC areas.

In 15 years, we anticipate that education will be based to a significant extent on unifying principles in science and technology that are easier to understand and more valuable for the learner. The new NBIC science content will have been introduced and be available in about 50 percent of the public schools. A variety of new pedagogical tools will be widely available, based on new learning methods, using learning-enhancing devices developed by neuroscience in cooperation with information technology. The process of learning at home or school, either individually or in groups, will be faster and better because of the new methods, tools, and processes.

Statements and Visions

As in the other working groups, participants in the Science and Education group prepared statements offering strategies for transforming the current situation with respect to scientific unification and visions of what could be accomplished in 10 or 20 years. Several contributors examined the social and intellectual processes by which sciences and technologies converge (M. Gorman, J. Batterson and A. Pope, and Y. Bar-Yam); others focused on the special education opportunities offered by integrating sciences from the nanoscale (W. Tolles and A. Cohen); on fully involving human resources (D. Akins); and on enhancing human abilities using biological language (J. Klein-Seetharaman and R. Reddy).

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STATEMENTS

COMBINING THE SOCIAL AND THE NANOTECHNOLOGY: A MODEL FOR CONVERGING TECHNOLOGIES

Michael E. Gorman, University of Virginia

The National Science Foundation (NSF) is considering societal implications as the new field of nanotechnology emerges, rather than wait for major problems to occur before attempting a fix. This concern for ethics at the earliest stages of discovery and invention needs to be extended to converging technologies as well, a theme to which I will return. But at the outset, I will limit my remarks to nanotechnology, following up on the 2001 NSF meeting on this topic (Roco and Bainbridge 2001).

H. Glimell (2001) has discussed how new fields like nanotechnology create the need for work at the boundaries between fields:

> Consider for example molecular electronics compared with bio-nano (or the interface of biological and organic nano materials). The actors, nodes and connections to appear in the extension of these NSE subareas obviously constitute two very different networks of

> innovation. Nanoelectronics is being negotiated and molded in between two camps — the conservative mainstream of the microelectronics industry with its skepticism towards anything popping up as a challenger to the three-decade-old CMOS technology trajectory, and the camp committed to a scenario where that trajectory might come to its end within some five years from now. (Glimell 2001, 199)

Peter Galison (1997) uses the metaphor of a trading zone between different cultures to describe cooperative work at boundaries. One of his examples is the collaboration between physicists and engineers in the Radiation Laboratory at MIT during World War II: "Each of the different subcultures was forced to set aside its longer term and more general symbolic and practical modes of work in order to construct the hybrid of practices that all recognized as 'radar philosophy.' Under the gun, the various subcultures coordinated their actions and representations in ways that had seemed impossible in peacetime; thrown together they began to get on with the job of building radar" (Galison 1997, 827). Despite differences in training and expertise, engineers and physicists of varying backgrounds were able to trade important information.

The current debates about nanotechnology are signs of an expanded trading zone. As Etkowitz has pointed out (2001), the physical sciences need to find a way to emulate the success of the life sciences while avoiding the ethical and social problems that have emerged as genetically modified organisms hit the market. Hence, several extravagant promises have been made about nanotechnology, promises that lead to concerns about what would happen if these promises were fulfilled — if, for example, self-replicating nanobots were ever created. The hardest thing to predict about a new technology is the interaction effect it will have with other evolving social and technical systems.

Thomas Park Hughes, a historian of technology who has spent a lifetime studying the invention of large technological systems, discusses how reverse salients attract inventors: "A salient is a protrusion in a geometric figure, a line of battle, or an expanding weather front. As technological systems expand, reverse salients develop. Reverse salients are components in the system that have fallen behind or are out of phase with the others" (Hughes 1987, 73). In the 1870s, progress in telegraphy was hindered by the fact that only two messages could be sent down a single wire at the same time: the classic problem of bandwidth.

What are the reverse salients that attract researchers and funding to nanotechnology? One is Moore's Law, which reaches asymptote very quickly unless a way can be found to shrink integrated circuits to the nanoscale. This current reverse salient is an instance of a historical one. Earlier, vacuum tubes held up progress in computing. Transistors solved that problem, but then formed their own reverse salient as computing needs expanded to the point where "Production of the first 'second generation' (i.e., completely transistorized) computer — the control data CD 1604, containing 25,000 transistors, 100,000 diodes, and hundreds of thousands of resistors and capacitors — lagged hopelessly behind schedule because of the sheer difficulty of connecting the parts" (Reid 1984, 18). The apparent solution was miniaturization, but there were physical limits. The solution was to transform the problem: instead of building tiny transistors, create an integrated

circuit. Nanotechnology offers a similar way to transcend the limits of microchip technology.

Another reverse salient is mentioned by several of contributors to the 2001 Report on the Societal Implications of Nanoscience and Nanotechnology of the Nanoscale Science, Engineering, and Technology (NSET) of the National Science and Technology Council (Roco and Bainbridge 2001). This is the ability to study and emulate fine-grained cellular structures. "Follow the analogy of nature" is a common invention heuristic that depends on an intimate knowledge of nature. Bell used this heuristic to transform the telegraph reverse salient in the 1870s. Instead of an improved device to send multiple messages down a single wire, he created a device to transmit and receive speech, using the human ear as a mental model. Bell's telephone patent formed the basis for one of the great communications start-ups of all time, the Bell Telephone Corporation, which surpassed Western Union, the Microsoft of its day (Carlson 1994). Similarly, detailed understanding of cellular processes at the nanoscale will lead to new devices and technologies that may transform existing reverse salients.

A potential set of reverse salients that came up repeatedly in the 2001 NSET report are environmental problems like ensuring clean water and providing adequate energy.

The terrorist attacks on September 11 will create a new series of reverse salients, as we think about ways of using technology to stop terrorism — and also of protecting against misuses of technology that could contribute to terrorism. Research should be directed towards determining which aspects of these broad reverse salients can be converted into problems whose solutions lie at the nanoscale. One important goal of such research should be separating hype from hope.

Role of Practical Ethics Combined with Social Science

The focus of practical ethics is on collaboration among practitioners to solve problems that have an ethical component. Similarly, social scientists who work in science-technology studies typically establish close links to practice. There are four roles for practical ethics linked to social sciences:

- Prevention of undesirable side effects
- Facilitation of quality research in nanotechnology by social scientists
- Targeting of converging technology areas of social concern
- Incorporation of ethics into science education

Prevention of Undesirable Side Effects

What are the potential negative impacts of nanotechnology, as far as important segments of society are concerned? How can these be prevented? The 2001 NSET report made frequent reference to the negative press received by genetically modified organisms (GMOs) as exactly the kind of problem nanotechnology practitioners wish to avoid. Monsanto, in particular, has developed a variety of genetically modified seeds that improve farmer yields while reducing use of pesticides and herbicides. But Monsanto did not include consumers in its trading zone, particularly in Europe, where potential customers want GMO products labeled so they can decide whether to buy. The best prevention is a broad trading zone that includes potential users as well as interested nongovernmental organizations like

Greenpeace in a dialogue over the future of new nanotechnologies. Social scientists and practical ethicists can assist in creating and monitoring this dialogue.

A related area of concern is the division between the rich and poor, worldwide. If new nanotechnologies are developed that can improve the quality of life, how can they be shared across national boundaries and economic circumstances in ways that also protect intellectual property rights and ensure a sufficient return on investment? Consider, for example, the struggle to make expensive AIDS medications available in Africa. Again, proper dissemination of a new technology will require thinking about a broad trading zone from the beginning. Social scientists can help establish and monitor such a trading zone.

Nanotechnology offers potential national security benefits (Tolles 2001). It might be possible, for example, to greatly enhance the performance of Special Forces by using nano circuitry to provide each individual soldier with more information. However, there are limits to how much information a human being can process, especially in a highly stressful situation. This kind of information might have to be accompanied by intelligent agents to help interpret it, turning human beings into cyborgs (Haraway 1997). Kurzweil (1999) speculates that a computer will approximate human intelligence by about 2020. If so, our cyborg soldiers could be accompanied by machines capable of making their own decisions. It is very important that our capacity for moral decision-making keep pace with technology.

Therefore, practical ethicists and social scientists need to be involved in the development of these military technologies. For example, cognitive scientists can do research on how a cyborg system makes decisions about what constitutes a legitimate target under varying conditions, including amount of information, how the information is presented, processing time, and quality of the connection to higher levels of command. Practical ethicists can then work with cognitive scientists to determine where moral decisions, such as when to kill, should reside in this chain of command.

Military technology faces barriers to sharing that are much higher than intellectual property concerns. The cyborg soldier is much more likely to come from a highly developed country and face a more primitive foe. However, technological superiority does not guarantee victory — nor does it guarantee moral superiority. Practical ethicists and social scientists need to act as stand-ins for other global stakeholders in debates over the future of military nanotechnology.

Facilitation of Quality Research in Nanotechnology by Social Scientists

Improving the quality of research is one area of convergence between the nano and the cogno. Cognitive scientists can study expertise in emerging technological areas and can help expert nanotechnology practitioners monitor and improve their own problem-solving processes. Experts rely heavily on tacit knowledge, especially on the cutting-edge areas (Gorman n.d.). Portions of this knowledge can be shared across teams; other portions are distributed, with individuals becoming experts in particular functions. Cognitive scientists can help teams reflect on this division of labor in ways that facilitate collaboration and collective learning (Hutchins 1995). Cognitive methods can therefore be used to study and improve multidisciplinary convergence, including the development of new trading zones.

Targeting of Converging Technology Areas of Social Concern

Practical ethics and social sciences should not be limited to anticipating and preventing problems. Both can play an important role in facilitating the development of nanotechnology, by encouraging reflective practice (Schon 1987).

An important goal of this reflection is to eliminate the compartmentalization between the technical and the social that is so predominant in science and engineering (Gorman, Hertz et al. 2000). Most of the engineers and applied scientists I work with are solutions seeking problems. They are generally people of personal integrity who, however, do not see that ethics and social responsibility should be factors in their choice of problems. Technology can evolve without improving social conditions, but true technological progress requires social progress. Indeed, focusing on social benefits opens up a range of interesting new technological problems.

Practical ethicists can work with engineers and scientists to identify interesting and worthy social concerns to which the latest developments in nanotechnology could be applied. Philosophers and social scientists cannot simply dictate which problems practitioners should try to solve, because not all social problems will benefit from the application of nanotechnology, and not all future technologies are equally likely.

Directing a technology towards a social problem does not eliminate the possibility of undesirable side effects, and a technology designed to produce harm may have beneficial spin-offs. For example, Lave (2001) does an admirable job of discussing the possibility of unforeseen, undesirable effects when nanotechnology is applied to environmental sustainability. The probability of truly beneficial environmental impacts is increased by taking an earth systems perspective (Allenby 2001). Similar high-level systems perspectives are essential for other nanotechnology applications; in order to achieve this kind of perspective, scientists, engineers, ethicists, and social scientists will have to collaborate.

Incorporation of Ethics into Science Education

How can practical ethicists and social scientists work with science and engineering educators to turn students into reflective nanotechnology researchers? I am Chair of a Division of Technology, Culture, and Communication at the University of Virginia, inside the Engineering School, which gives us a great opportunity to link social responsibility directly to engineering practice. We rely heavily on the case method to accomplish this (Gorman, Mehalik, et al. 2000). We also co-supervise every engineering student's senior thesis; we encourage students to think about the social impact of their work. But we need to go a step further and encourage more students to pursue work linking the social, the ethical, and the technical.

This kind of linkage can attract students into engineering and science, especially if this sort of education is encouraged at the secondary level. Unfortunately, our secondary and elementary educational systems are now focused more on the kind of accountability that can be measured in examinations and less on the kind of creativity and perseverance that produces the best science and engineering. New educational initiatives in nanotechnology can play an important role in changing this climate.

A New Kind of Engineering Research Center

Several years ago, NSF sponsored an Engineering Research Center (ERC) that combined bioengineering and educational technology. Why not also sponsor an ERC that combines research and teaching on the societal implications of nanotechnology? Parts of this center could be distributed, but it should include one or more nanotechnology laboratories that are willing to take their fundamental science and apply it in directions identified as particularly beneficial by collaborating social scientists and practical ethicists. The goal would be "to infuse technological development with deeper, more thoughtful and wide-ranging discussions of the social purposes of nanotechnology…putting socially beneficial technologies at the top of the research list" (Nardi 2001, 318-19). Deliberations and results should be shared openly, creating an atmosphere of transparency (Weil 2001).

This center could combine graduate students in science and engineering with those trained in social sciences and ethics, thus forming a "living bridge" connecting experts from a variety of disciplines. Some graduate students could even receive training that combines engineering, ethics, and social sciences, as we do in a graduate program at the University of Virginia (Gorman, Hertz, et al. 2000).

The center should hold annual workshops bringing other ERCs and other kinds of research centers involved with nanotechnology together with applied ethicists and social scientists. There should be a strong educational outreach program designed to encourage students concerned with making the world a better place to consider careers in nanotechnology. Hopefully, the end-result would be a model for creating trading zones that encourage true technological progress.

This kind of a center need not be limited to nanotechnology. What about a science and technology center on the theme of converging nano, bio, info and cogno (NBIC) technologies directed towards maximum social benefit? One example of a potential NBIC product is of a smart agent able to look up the price and availability of a particular item and identify the store where it can be found while a consumer walks through the mall. This kind of technology has no benefits for the millions all over the world who are dying of AIDS, suffering from malnutrition, and/or being oppressed by dictators.

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BREADTH, DEPTH, AND ACADEMIC NANO-NICHES

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The report to the President titled *Science: The Endless Frontier* (Bush 1945) ushered in a period of rapid growth in research for two to three decades. This was stimulated further by the launch of Sputnik and programs to explore the moon. Over the past 56 years, research has moved from an environment where there was unquestioned acceptance of academic-style research by both academia and industry to an environment in which industry, in its effort to maintain profit margins in the face of global competition, has rejected the academic model of research and now focuses on short-term objectives. The need for industry to hire new blood and to generate new ideas is a major stimulus for cooperation between industry and academia. Academia has mixed reactions to these more recent trends. Universities are concerned about a loss of some independence and freedom to pursue new ideas in conjunction with industry, primarily due to the proprietary nature of maturing research/development. The pressures on academia to "demonstrate relevance" have continued for decades. In the search for "relevance," the concept of nanotechnology has emerged to satisfy a large community of researchers in both academia and industry.

The discovery of a new suite of experimental tools (beginning with scanning tunneling microscopy) with which to explore ever smaller features, to the level of the atom, reopened the doors joining the progress of academia to that of industry. The nanotechnology concept fulfilled the pressures of both the commercial world (pursuing continuation of the fruits of miniaturization) and academia (pursuing opportunities to research the many new pathways opened by these tools). The umbrella term "nanotechnology" covers programs already underway in both communities, thus giving a stamp of approval to many existing efforts. The goals and expectations of nanotechnology have been chosen in such a way that the march of the science and technology will yield new systems in many technological markets. There is little chance of disappointing the public (and Congress), due to the productivity of these endeavors. Yet, there appears to be more to the umbrella term than simply a new label for existing research directions. It has generated a new stimulus for academic pursuits in subtle ways that will have a lasting impact on our educational system.

Depth and Breadth a Bonus for Nanotechnology in Academia

University graduates must have skills in depth within a particular subject, a necessary aspect of pursuing the frontier of new knowledge with sufficient dedication to advance these frontiers. Yet, industry, concerned with satisfying consumers, is responsive to new opportunities that continually change. A university graduate may offer just what a given industrial position desires at a given time, but inevitable change may render those skills obsolete. Choosing new research directions more often, even within academic endeavors, is an inevitable part of a world characterized by rapidly expanding frontiers of new knowledge. *Depth* is an essential ingredient in the university experience, but *breadth* provides for greater flexibility when change occurs. The challenge to academia is to retain its strength in creating new knowledge while offering increasingly important breadth in its educational programs. Pursued separately, adding breadth to a student's experience can be satisfied by extending the time on campus, but this is costly and not particularly productive towards developing new knowledge, one of the primary goals of academia. Both professors and students are reluctant to substitute nondisciplinary courses in a curriculum already heavily laden with disciplinary material. What would be ideal in the academic experience would be to introduce *breadth* while simultaneously pursuing *depth*.

The subject of nanotechnology offers this opportunity, due to the multidisciplinary nature of the field. Researcher #1 in the field of chemistry or physics, for example, may wish to obtain knowledge of the structure of self-assembled particles, which may be of interest to researcher #2 in the field of electronics, who is interested in examining ways to fabricate quantum dots or novel structures for transistors. This is but one small example of the many opportunities that arise for joint objectives bridging disciplines. Such opportunities are labeled "nano-niches." These situations offer the student not only the opportunity to examine a phenomenon in depth, but to exchange results with similar activities in neighboring fields, where new perspectives may be obtained about other disciplines with relatively little additional effort (see schematic in Figure F.1).

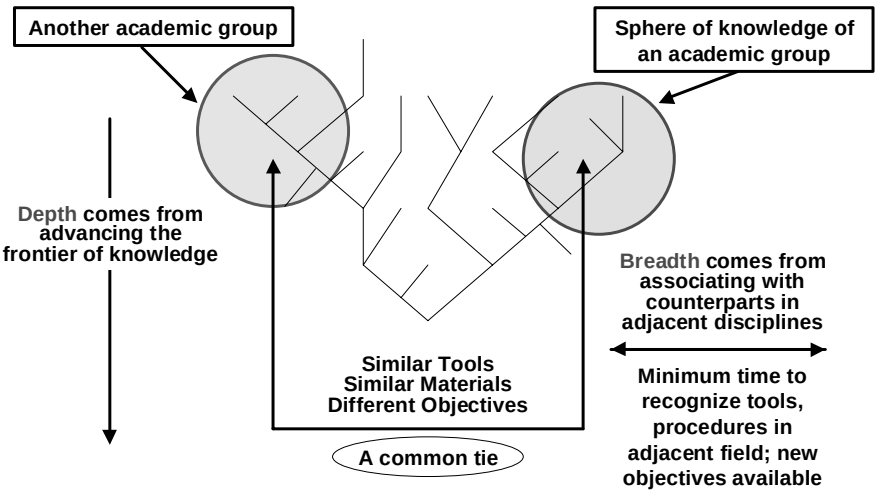

Figure F.1. Nanotechnology offers hope of depth plus breadth.

The value of multidisciplinary research has been extolled for years. However, it is impossible to have multidisciplinary research without having disciplines! Organizational changes that universities are now introducing include structures that encourage multidisciplinary pursuits, with consequent benefits to the student and the educational process. Breadth may be introduced by pursuing research objectives that have common features across disciplinary lines and by associating with more than one discipline. By encouraging "social interaction" (use of common instrumentation, materials, and theory) with peers in neighboring disciplines, the related frontiers in other disciplines may be easily introduced. This provides a graduate with stronger career opportunities, having the combined ability to pursue research in depth, but also having the ability to recognize additional options when the inevitable need for alternate opportunities arises.

Sharing expensive instrumentation in a common facility is one way to stimulate overlap of the academic disciplines, and this has been introduced extensively for nanotechnology. The National Nanofabrication Users Network (http://www.nnun.org/) consists of instrumentation centers at five major universities. A number of centers and institutes (http://www.nano.gov/centers.htm) have been introduced that stimulate the overlap of disciplines pursuing common goals. These organizations focus on objectives such as chemical and biological sensors, electron transport in molecules, nanoelectronics, assembly of nanostructures, and nanoscale devices/systems and their applications. These "academic nano-niches" are already established, and they will generate the benefits of multidisciplinary programs, with the concurrent advantages of depth and breadth. Other means of stimulating overlap involve common courses, seminars, and temporary exchanges of personnel.

Vision in Nanotechnology: How to Achieve it

One virtue of multidisciplinary research is the introduction of more comprehensive goals that may be achieved by several interactive research programs. A statement of these goals, along with the consequences, is frequently referred to as

"vision." Occasionally, a research group sets out to conquer the larger goals with approaches that worked well with the previous in-depth methodology alone. That is, they pursue a larger goal with limited knowledge of the full picture. With the urgent need for faculty to obtain research funds, less time is available to examine the full picture associated with some of these larger goals. Some directions chosen by groups with a limited perspective may ignore the wisdom of more experienced communities. This problem is more severe when goals include "legions" of researchers from many disciplines, such as those currently being pursued by the computer industry.

Thus, the call for vision has generated its own unease in the midst of these transformations. Articulating a vision is tricky. As Yogi Berra stated, "*It's tough to make predictions, especially about the future*" (http://www.workinghumor.com/quotes/yogi_berra.shtml). This difficulty has been exacerbated by the introduction of virtual reality. Images can be readily drawn that conjure phenomena totally inconsistent with the world of reality. When applied to apparent scientific problems, misperceptions may result in groups expounding concepts they do not understand; perceptions may even violate the usual laws of physics (or related constraints recognized through years of experience).

Nevertheless, vision statements are important for the research world, and Congressional appropriations for research are increasingly tied to (1) a linear extrapolation of past success and (2) visions that portend significant impact for the nation. The concepts associated with nanotechnology support these criteria in many ways. Most notably, enhanced electronics, enhanced medical diagnostics, improved medical procedures, and new materials are major areas that meet these two criteria. Stating a goal, pursuing it, and reaching it generate credibility. This is achieved best by those well versed in scientific principals and methods and the ramifications of potential paths to be pursued. It is not achieved by visionaries who appear to understand the world only through the images of virtual reality, without the sound knowledge of the basic principles drawn from the experimental world and experience with the perversity of Mother Nature. In addition, although serendipity has its place, it is not to be depended upon for productivity in research or for setting goals at the initiation of a program. The plethora of paths to follow in research exceeds by far the number of researchers. Consequently, a judicious choice of directions is essential, and the process of choosing these goals is vitally important to the health of the enterprise.

In light of the controversy surrounding discussion of the hazards of the so-called "self-replicating nanobots" (Tolles 2001, 173), a few words of caution seem in order. The nanotechnology community should show some restraint when releasing articles to the press about any major impact on an already established field. Setting scientific goals that may be achieved within a career (or within a decade) seems preferable to choosing goals that appear incompatible with the behavior of the physical world. The hazards of the so-called "self-replicating nanobots" seem to have already generated far more discussion than they warrant (Tolles 2001). Visions of ultra-fast and powerful computers the size of poppy seeds conjure unrealistic expectations, feeding further the fears that the products of our creation may be smarter than we are and that we may sow the seeds of our own destruction. "*The rub in exploring the borderlands is finding that balance between being open-minded*

enough to accept radical new ideas but not so open-minded that your brains fall out" (Shermer 2001, 29). We must recognize that it is difficult to predict the future; in particular, there is no reason to raise hopes for a device or a phenomenon that violates the basic laws of physics and chemistry. Another perspective: "*... the burden of proof is not on those who know how to make chips with 10^7 transistors and connect them together with millions of wires, it is up to those who show something in a laboratory to prove that it is better*" (Keyes 2001b).

The Academic Nano-Niches

Several "nano-niches" that appear most obvious today are outlined below. There are, of course, many other concepts emerging from the fertile frontier of miniaturization that are not easily categorized. Perhaps other significant niches will emerge in this new dimension of material control and behavior.

Nano-Niche #1

Objectives for enhancing electronic devices have been the basis for many nanotechnology programs. The nanotechnology efforts in programs such as molecular electronics have been pursued for decades with little impact on the electronics industry thus far. The more conservative microelectronics industry continues to pursue CMOS and is skeptical of radically new ideas that may deviate from its International Technology Roadmap for Semiconductors (ITRS) (Semiconductor Industry Association 2001) for a number of years in the future (Glimmell 2001). This is one area of nanotechnology that could benefit from a significant overlap with expertise in the electronics and information technology communities. Goals of forming molecular computers have appeared in a number of places. The physical realities one must meet to achieve such goals have been mentioned in a number of papers (e.g., Keyes 2001a; Meindl 1995, 1996; Meindl, Chen, and Davis 2001; Semiconductor Industry Association 2001). Molecular transistors have recently been fabricated (Bachtold et al. 2001; Schön, Meng, and Bao 2001). They have even been incorporated into circuits that can be used for logic operations (Bachtold et al. 2001). The challenges facing this nano-community now are very similar to those facing the semiconductor industry (see the Roadmap). These two communities will begin to work together cooperatively for a common goal. Innovative methods for incorporating new nanostructures into more conventional circuits will probably be the outcome of these interactions. The chemical and biological influences on the nanostructure of semiconductors is just beginning to be recognized (Whaley et al. 2000). Of course, alternative architectures for computational tasks represent a likely path for new breakthroughs. The brain of living species represents proof that such alternative architectures exist. It is through the innovation of these communities that such advances are likely to be introduced.

Nano-Niche #2

Research in nanostructures associated with biomolecular science is well recognized and proves to be a fertile field for a nano-niche. Biomolecules are often large and qualify as "nanostructures." Introduction of the tools and experience of chemists and physicists, even electrical engineers, in pursuing this mainstream of nanotechnology offers many opportunities for the synergism of multidisciplinary research in biology, biotechnology, and medicine. A biology student pursuing

research with the tools of nanotechnology enters biomedical frontiers that include ability to fabricate sensors for the rapid, inexpensive detection of environmental hazards and disease organisms and to fabricate biomolecules with an objective to target selective cells (such as cancer cells) for modification of their function (Alivisatos 2001). Miniature chemistry laboratories are being fabricated on chips. These tools are likely to find applications in the task of sequencing genetic codes, of importance for medical purposes. This nano-niche includes the disciplines of chemistry, physics, biomolecular engineering, and even electrical engineering. One caution is worth noting. The ability to create new microbes, viruses, etc., in this field could lead to new biological species that present risks. As stated elsewhere, "The main risks for negative societal implications of nanotechnology will probably continue to be in the area of biotechnology rather than electronics" (Doering 2001, 68).

Nano-Niche #3

The field of materials science has always been a multidisciplinary endeavor. This is no less true for materials composed of nanostructures. One recent article points out the value of porous silicon as a stimulus to educational opportunities in electronics, optoelectronics, microoptics, sensors, solar cells, micromachining, acoustics, medicine, biotechnology, and astrophysics (Parkhutik and Canham 2000). A new material may be prepared using a variety of fabrication techniques from a number of disciplines and find applications in a number of technologies, accounting for the value of such a field for introducing breadth to the student experience. Of course, the depth from such an endeavor comes from advancing the knowledge about a given material using the tools from various scientific disciplines. Since new materials are of interest due to the possible substitution in an existing science or technology, the multidisciplinary aspect of materials will always exist.

Nanotechnology as a Stimulus to Inquiring Minds

As a stimulus for education in the sciences, nanotechnology has led to a wealth of fascinating scientific revelations. Attracting young inquiring minds has been the subject of an NSF-supported consortium project at Arizona State University in conjunction with other universities. This project, Interactive Nano-Visualization in Science and Engineering Education (IN-VSEE), may be viewed at http://invsee.asu.edu/. The goal of this program is to bring the excitement of discovery with electron and scanning tunneling microscopy into the classroom, targeting students in upper-level high school through college. At this level, the attraction of the multidisciplinary aspects is obvious. The subject of nanotechnology as a basis to illustrate scientific principals is likewise clear.

Summary

In summary, nanotechnology provides an impetus for transforming the academic experience, introducing a new stimulus for breadth in the career of a student while minimizing the additional time to assimilate that breadth. The historical functions of creating new knowledge through in-depth study need not be compromised with such programs. Programs in nanotechnology represent excellent areas of research to demonstrate this and will be one basis for a subtle transformation of the academic environment. Philosophers, business schools, psychologists, and many of the "soft

sciences" may debate the implications of nanotechnology. However, without a realistic view of what may be expected from this fertile research frontier, there may be unnecessary discussions about unrealistic expectations. Information released to the media and studies of a social nature should follow careful assessments by technically qualified research teams presenting rational projections for the future potential of this fascinating field.

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UNIFYING PRINCIPLES IN COMPLEX SYSTEMS

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The ability of science and technology to augment human performance depends on an understanding of systems, not just components. The convergence of technologies is an essential aspect of the effort to enable functioning systems that include human beings and technology, serving the human beings to enhance their well-being directly and indirectly through what they do and what they do for other human beings. The recognition today that human beings function in teams rather than as individuals implies that technological efforts are essential that integrate human beings across scales of tools, communication, and biological and cognitive function.

Understanding the role of complex systems concepts in technology integration requires a perspective on how the concept of complexity is affecting science, engineering, and finally, technology integration.

Complex Systems and Science

The structure of scientific inquiry is being challenged by the broad relevance of complexity to the understanding of physical, biological, and social systems (Bar-Yam 2000; Bar-Yam and Minai 2002; Gallagher and Appenzeller 1999). Cross-disciplinary interactions are giving way to transdisciplinary and unified efforts to address the relevance of large amounts of information to describing, understanding, and controlling complex systems. From the study of biomolecular interactions (Service 1999; Normile 1999; Weng, Bhalla, and Iyengar 1999) to the strategy tactics of 21st century Information Age warfare and the war on terrorism, complexity has arisen as a unifying description of challenges to understanding and action. In this arena of complex systems, information, and action, structure and function are entangled. New approaches that recognize the importance of patterns of behavior, the multiscale space of possibilities, and evolutionary or adaptive processes that select systems or behaviors that can be effective in a complex world are central to advancing our understanding and capabilities (Bar-Yam 1997).

Complex Systems and Engineering

The failure of design and implementation of a new air traffic control system, failures of Intel processors, medical errors (IOM 2000), failures of medical drugs, even the failure of the Soviet Union, can be described as failures of large, complex systems. Systematic studies of large-scale engineering projects have revealed a remarkable proportion of failures in major high-investment projects. The precursors of such failures (multisystem integration, high-performance constraints, many functional demands, high rates of response, and large, context-specific protocols), are symptomatic of complex engineering projects. The methods for addressing and executing major engineering challenges must begin from the recognition of the role of complexity and the specific tools that can guide the design, or self-organization, of highly complex systems. Central to effective engineering are evaluation of the complexity of system functions; recognition of fundamental engineering tradeoffs of structure, function, complexity, and scale in system capabilities; and application of

indirection to specification, design, and control of system development and the system itself.

Defining Complex Systems and Complex Tasks

One way to define a complex task is as a problem where the number of distinct possibilities that must be considered, anticipated, or dealt with is substantially larger than can be reasonably named or enumerated. We can casually consider in an explicit way tens of possibilities, a professional can readily deal with hundreds of possibilities, and a major project deals with thousands. The largest projects deal with tens of thousands. For larger numbers of possibilities, we must develop new strategies (Bar-Yam 1997). Simplifying a complex task by ignoring the need for different responses is what leads to errors or failures that affect the success of the entire effort, leaving it as a gamble with progressively higher risks.

The source of complex tasks is complex systems. Complex systems are systems with interdependent parts. Interdependence means that we cannot identify the system behavior by just considering each of the parts and combining them. Instead we must consider how the relationships between the parts affect the behavior of the whole. Thus, a complex task is also one for which many factors must be considered to determine the outcome of an action.

Converging Technologies

The rapid development of nanotechnology and its convergence with biological, information, and cognitive sciences is creating a context in which complex systems concepts that enable effective organizations to meet complex challenges can be realized through technological implementation. At the same time, complex systems concepts and methods can describe the framework in which this convergence is taking place. From the fine-scale control of systems based upon nanotechnology to understanding the system properties of the integrated socio-technical system consisting of human beings and computer information networks, the synergy of complex systems theory and converging technologies is apparent as soon as we consider the transition between components and functions.

Looking Forward

Human civilization, its various parts (including its technology), and its environmental context may be described as complex. The most reliable prediction possible is that this complexity will continue to increase. The great opportunity of the convergence of nanotechnology, biomedical, information, and cognitive sciences is an explosive increase in what is possible through combining advances in all areas. This is, by definition, an increase in the complexity of the systems that will be formed out of technology and of the resulting behaviors of people who use them directly or are affected by them. The increasing complexity suggests that there will be a growing need for widespread understanding of complex systems as a counterpoint to the increasing specialization of professions and professional knowledge. The insights of complex systems research and its methodologies may become pervasive in guiding what we build, how we build it, and how we use and live with it. Possibly the most visible outcome of these developments will be an improved ability of human beings, aided by technology, to address global, social, and environmental problems: third world development, poverty in developed

countries, war, and natural disasters. At an intermediate scale, the key advances will dramatically change how individuals work together in forming functional teams that are more directly suited to the specific tasks they are performing. In the context of individual human performance, the key to major advances is recognizing that the convergence of technology will lead to the possibility of designing (or, more correctly, adapting) the environment of each individual for his or her individual needs and capabilities in play and work.

The Practical Need

Complex systems studies range from detailed studies of specific systems to studies of the mechanisms by which patterns of collective behaviors arise, to general studies of the principles of description and representation of complex systems. These studies are designed to enable us to understand and modify complex systems, design new ones for new functions, or create contexts in which they self-organize to serve our needs without direct design or specification. The need for applications to biological, cognitive, social, information, and other engineered systems is apparent.

Biology has followed an observational and reductionistic approach of accumulating large bodies of information about the parts of biological systems and looking for interpretations of system behavior in terms of these parts. It has become increasingly clear that biological systems are intricate, spatially structured, biochemically based networks. The role of information in biological action and the relationships of structure and function are only beginning to be probed by mathematicians, physicists, and engineers who are interested in biological systems as systems designed by nature for their functional capabilities. While biologists are increasingly looking to mathematical approaches and perspectives developed in physics and engineering, engineers are increasingly looking to biological systems for inspiration in designing artificial systems. Underlying these systems are a wealth of design principles in areas that include the biochemical networks (Gallagher and Appenzeller 1999; Service 1999; Normile 1999; Weng, Bhalla, and Iyengar 1999); immune systems (Perelson and Wiegel 1999; Noest 2000; Segel and Cohen 2001; Pierre et al. 1997) and neural systems (Anderson and Rosenfeld 1988; Bishop 1995; Kandel, Schwartz, and Jessell 2000); and animal behaviors such as the swimming mechanisms of fish (Triantafyllou and Triantafyllou 1995) and the gaits of animals (Golubitsky et al. 1999). These systems and architectures point to patterns of function that have a much higher robustness to failure and error and a higher adaptability than conventional human engineered systems.

Computers have made a transition from systems with tightly controlled inputs and outputs to systems that are networked and respond on demand as part of interactive information systems (Stein 1999). This has changed radically the nature of the issues facing their design. The collective behaviors of these networked computer systems, including the Internet, limit their effectiveness. Whether these have to do with the dynamics of packet loss in Internet traffic or the effect of computer viruses or worms (Forrest, Hofmeyr, and Somayaji 1997; Kephart et al. 1997; Goldberg et al. 1998), that at times have incapacitated a large fraction of the Internet, these effects are not small. The solution to these problems lies in understanding collective behaviors and in designing computer systems to be

effective in environments with complex demands and to have higher defensive robustness.

The human brain is often considered the paradigmatic complex system. The implications of this recognition are that cognitive function is distributed within the brain, and mechanisms may vary from individual to individual. Complete explanations of cognitive function must themselves be highly complex. Major advances in cognitive science are currently slowed by a combination of efforts on the one hand to explain cognitive function directly from the behavior of individual molecular and cellular components, and on the other hand to aggregate or average the cognitive mechanisms of different human beings. Still, diverse advances that are being made are pointing the way to improvements in education (NIMH 2002), man-machine interfaces (Norman and Draper 1986; Nielsen 1993; Hutchins 1995), and retention of capabilities during aging (Stern and Carstensen 2000; Mandell and Schlesinger 1990; Davidson, Teicher, and Bar-Yam 1997).

The recognition of the complexity of conflict in the war on terrorism is another indication that the basic concept of complexity in social systems or problems has begun to be recognized. Unfortunately, this understanding has yet to be transferred to address other diverse major fundamental social system problems, as found in medical system cost containment, education system reform, and alleviation of poverty. In each case, current approaches continue to be dominated by large-scale strategies that are ineffective in addressing complex problems. Even with the appearance of more holistic approaches to, for example, third world development (World Bank 1998), the basic concept of existing strategy remains weakly informed by complex systems insights. This gap is an opportunity for major contributions by the field of complex systems at both the conceptual and technical levels. Further contributions can be made based upon research projects that emphasize the intrinsic complexity of these systems.

Understanding complex global physical and biological systems is also a major challenge. Many key problems today have to do with indirect effects of human activities that may have substantial destructive effects on the human condition. These include global warming and ecological deterioration due to overexploitation of resources. Effective approaches to these problems require understanding both the environmental and socioeconomic implications of our current actions and of actions that are designed to alleviate these problems (NSF n.d.). For example, the problem of global warming includes the effects of large-scale human activity interacting with both the linear and potentially nonlinear climactic response. Despite the grave risks associated with global warming, a key factor impeding actions to alleviate it is fear of major impacts of such efforts on socioeconomic systems. Better understanding of the potential effects of such interventions should enable considered actions to be taken.

Interest

Study of complex systems has become recognized as a basic scientific endeavor whose inquiry has relevance to the management of complex organizations in a complex world (Herz 2001). More specific attention has been gained in information technology (Horn 2001), biotechnology (Strausberg and Austin 1999; NSF n.d.; NIGMC n.d.; NSF 2001), healthcare industries, and the military.

Information technology companies building computer hardware and software have begun to recognize the inherently interactive and distributed nature of the systems they are designing. A significant example is the IBM "Autonomic Computing" initiative (Horn 2001), which is inspired by the biological paradigm of the autonomic nervous system and is conceptually based upon modeling robustness through biologically inspired system design. In a different perspective, Apple Computer has demonstrated the relevance of human factors, ranging from hardware design to ease-of-use and facilitation of creativity, as essential aspects of the role of computers in computer-human systems.

The major advances in biotechnology, including the genome project and other high-throughput data acquisition methods, have led to a dramatic growth in the importance of modeling and representation tools to capture large bodies of information and relate them to system descriptions and properties. Many private companies at the forefront of biotechnology are developing bioinformatics tools that strive to relate information to functional descriptions also described as "functional genomics" (Srausberg and Austin 1999). This is one facet of a broader recognition of the importance of capturing the multiscale properties of biological systems as reflected in NSF's biocomplexity initiative (NSF n.d.) and the complex biological systems programs at NIH (NIGMS 2002), as well as in joint programs.

For several years, the interest in complex systems as a conceptual and quantitative management tool has led consulting companies to work on practical implementations of strategy and more specific modeling efforts (Ernst and Young 2000, Gleick 1987). One of the areas of particular interest has been in the healthcare management community, where rapid organizational change has led to a keen interest in complex systems insights.

In the military and intelligence communities, there has been increasing realization of the relevance of networked distributed control and information systems. All branches of the military and the joint chiefs of staff have adopted vision statements that focus on complex systems concepts and insights as guiding the development of plans for information age warfare. These concepts affect both the engineering of military sensors, effectors, and information networks, and the underlying nature of military force command and control.

More broadly, the public's attention has been widely attracted to the description of complex systems research and insights. Indeed, many popular descriptions of complex systems research existed before the first textbook was written (Gleick 1987; Lewin 1992; Waldrop 1992; Gell-Mann 1994; Casti 1994; Goodwin 1994; Kauffman 1995; Holland 1995; Coveney and Highfield 1995; Bak 1996). The excitement of scientists as well as the public reflects the potential impact on our ability to understand questions that affect everyday life, perspectives on the world around us, fundamental philosophical disputes, and issues of public concern such as major societal challenges, the dynamics of social networks, global computer networks (the WWW), biomedical concerns, psychology, and ecology.

The Goals

The goals of complex systems research are to understand the following:

- Understand the development and mechanisms of patterns of behavior and their use in engineering

- Understand the way to deal with complex problems (engineering, management, economic, sociopolitical) using strategies that relate the complexity of the challenge to the complexity of the system that must respond to them
- Understand the unifying principles of organization, particularly for systems that deal with large amounts of information (physical, biological, social, and engineered)
- Understand the interplay of behaviors at multiple scales and between the system and its environment
- Understand what is universal and what is not, when averaging applies and when it does not, what can be known and what cannot, what are the classes of universal behavior and the boundaries between them, and what are the relevant parameters for describing or affecting system behaviors
- Develop the ability to capture and represent specific systems rather than just accumulate data about them: (in this context) to describe relationships, know key behaviors, recognize relevance of properties to function, and simulate dynamics and response.
- Achieve a major educational shift toward unified understanding of systems and patterns of system behavior.

The traditional approach of science of taking things apart and assigning the properties of the system to its parts has been quite successful, but the limits of this approach have become apparent in recent years. When properties of a system result from dependencies and relationships but we assign them to their parts, major obstacles arise to understanding and control. Once the error of assignment is recognized, some of the obstacles can be overcome quickly, while others become subjects of substantive inquiry. Many scientists think that the parts are universal but the way parts work together is specific to each system. However, it has become increasingly clear that how parts work together can also be studied in general, and by doing so, we gain insight into every kind of system that exists, including physical systems like the weather as well as biological, social, and engineered systems.

Understanding complex systems does not mean that we can predict their behavior exactly; it is not just about massive databases or massive simulations, even though these are important tools of research in complex systems. The main role of research in the study of complex systems is recognizing what we can and cannot say about complex systems given a certain level (or scale) of description and knowing how we can generalize across diverse types of complex systems. It is just as important to know what we can know, as to know. Thus the concept of deterministic chaos appears to be a contradiction in terms: how can a deterministic system also be chaotic? It is possible because there is a rate at which the system behavior becomes dependent on finer and finer details (Cvitanovic 1989; Strogatz 1994; Ott 1993). Thus, how well we know a system at a particular time determines how well we can predict its behavior over time. Understanding complexity is neither about prediction or lack of predictability, but rather a quantitative knowledge of how well we can predict, and only within this constraint, what the prediction is.

Fundamental Research in Complex Systems: Theorems and Principles

Fundamental research in complex systems is designed to obtain characterizations of complex systems and relationships between quantities that characterize them. When there are well-defined relationships, these are formalized as theorems or principles. More general characterizations and classifications of complex systems are described below in major directions of inquiry. These are only a sample of the ongoing research areas.

A theorem or principle of complex systems should apply to physical, biological, social, and engineered systems. Similar to laws in physics, a law in complex systems should relate various quantities that characterize the system and its context. An example is Newton's second law that relates force, mass, and acceleration. Laws in complex systems relate qualities of system, action, environment, function, and information. Three examples follow.

Functional Complexity

Given a system whose function we want to specify, for which the environmental (input) variables have a complexity of $C(e)$, and the actions of the system have a complexity of $C(a)$, then the complexity of specification of the function of the system is

$$C(f)=C(a)\,2^{C(e)}$$

where complexity is defined as the logarithm (base 2) of the number of possibilities or, equivalently, the length of a description in bits.

The proof follows from recognizing that complete specification of the function is given by a table whose rows are the actions (C(a) bits) for each possible input, of which there are $2^{C(e)}$. Since no restriction has been assumed on the actions, all actions are possible, and this is the minimal length description of the function. Note that this theorem applies to the complexity of description as defined by the observer, so that each of the quantities can be defined by the desires of the observer for descriptive accuracy. This theorem is known in the study of Boolean functions (binary functions of binary variables) but is not widely understood as a basic theorem in complex systems (Bar-Yam 1997).

The implications of this theorem are widespread and significant to science and engineering. The exponential relationship between the complexity of function and the complexity of environmental variables implies that systems that have environmental variables (inputs) with more than a few bits (i.e., 100 bits or more of relevant input) have functional complexities that are greater than the number of atoms in a human being and thus cannot be reasonably specified. Since this is true about most systems that we characterize as "complex," the limitation is quite general. The implications are that fully phenomenological approaches to describing complex systems, such as the behaviorist approach to human psychology, cannot be successful. Similarly, the testing of response or behavioral descriptions of complex systems cannot be performed. This is relevant to various contexts, including testing computer chips, and the effects of medical drugs in double-blind population studies. In each case, the number of environmental variables (inputs) is large enough that all cases cannot be tested.

Requisite Variety

The Law of Requisite Variety states that the larger the variety of actions available to a control system, the larger the variety of perturbations it is able to compensate (Ashby 1957). Quantitatively, it specifies that a well-adapted system's probability of success in the context of its environment can be bounded:

$$-\text{Log}_2(P) < C(e) - C(a)$$

Qualitatively, this theorem specifies the conditions in which success is possible: a matching between the environmental complexity and the system complexity, where success implies regulation of the impact of the environment on the system.

The implications of this theorem are widespread in relating the complexity of desired function to the complexity of the system that can succeed in the desired function. This is relevant to discussions of the limitations of specific engineered control system structures, of the limitations of human beings, and of human organizational structures.

Note that this theorem, as formulated, does not take into account the possibility of avoidance (actions that compensate for multiple perturbations because they anticipate and thus avoid the direct impact of the perturbations), or the relative measure of the space of success to that of the space of possibilities. These limitations can be compensated for.

Non-averaging

The Central Limit Theorem specifies that collective or aggregate properties of *independent* components with bounded probability distributions are Gaussian, distributed with a standard deviation that diminishes as the square root of the number of components. This simple solution to the collective behavior of non-interacting systems does not extend to the study of interacting or interdependent systems. The lack of averaging of properties of complex systems is a statement that can be used to guide the study of complex systems more generally. It also is related to a variety of other formal results, including Simpson's paradox (Simpson 1951), which describes the inability of averaged quantities to characterize the behavior of systems, and Arrow's Dictator Theorem, which describes the generic dynamics of voting systems (Arrow 1963; Meyer and Brown 1998).

The lack of validity of the Central Limit Theorem has many implications that affect experimental and theoretical treatments of complex systems. Many studies rely upon unjustified assumptions in averaging observations that lead to misleading, if not false, conclusions. Development of approaches that can identify the domain of validity of averaging and use more sophisticated approaches (like clustering) when they do not apply are essential to progress in the study of complex systems.

Another class of implications of the lack of validity of the Central Limit Theorem is the recognition of the importance of individual variations between different complex systems, even when they appear to be within a single class. An example mentioned above is the importance of individual differences and the lack of validity of averaging in cognitive science studies. While snowflakes are often acknowledged as individual, research on human beings often is based on assuming their homogeneity.

More generally, we see that the study of complex systems is concerned with their universal properties, and one of their universal properties is individual differences.

This apparent paradox, one of many in complex systems (see below), reflects the importance of identifying when universality and common properties apply and when they do not, a key part of the study of complex systems.

Major Directions of Inquiry

How Understanding Self-Organization & Pattern Formation Can be Used to Form Engineered Systems

Self-organization is the process by which elements interact to create spatio-temporal patterns of behavior that are not directly imposed by external forces. To be concrete, consider the patterns of spontaneous traffic jams or heart beats. For engineering applications, the promise of understanding such pattern formation is the opportunity to use the natural dynamics of the system to create structures and impose functions rather than to construct them element by element. The robustness of self-organized systems is also a desired quality in conventional engineered systems — and one that is difficult to obtain. For biomedical applications, the promise is to understand developmental processes like the development of the fertilized egg into a complex physiological organism, like a human being. In the context of the formation of complex systems through development or through evolution, elementary patterns are the building blocks of complex systems. This is diametrically opposed to considering parts as the building blocks of such systems.

Spontaneous (self-organizing) patterns arise through symmetry breaking in a system when there are multiple inequivalent static or dynamic attractors. In general, in such systems, a particular element of a system is affected by forces from more than one other element, and this gives rise to "frustration" as elements respond to aggregate forces that are not the same as each force separately. Frustration contributes to the existence of multiple attractors and therefore of pattern formation.

Pattern formation can be understood using simple rules of local interaction, and there are identifiable classes of rules (universality) that give rise to classes of patterns. These models can be refined for more detailed studies. Useful illustrative examples of pattern forming processes are local-activation, long-range inhibition models that can describe patterns on animal skins, magnets, dynamics of air flows in clouds, wind-driven ocean waves, and swarm behaviors of insects and animals. Studies of spontaneous and persistent spatial pattern formation were initiated a half century ago by Turing (1952), and the wide applicability of patterns has gained increasing interest in recent years (Bar-Yam 1997; Meinhardt 1994; Murray 1989; Nijhout 1992; Segel 1984; Ball 1999).

The universality of patterns has been studied in statistical physics, where dynamic patterns arise in quenching to a first-order phase transition both in cases of conserved (spinodal decomposition, e.g., oil-water separation) and nonconserved (coarsening, e.g., freezing water) order parameters (Bray 1994) and also in growing systems (self-organized criticality, e.g., roughening). Generic types of patterns are relevant for such contexts and are distinguished by their spatio-temporal behaviors. Classic models have characteristic spatial scales (Turing patterns, coarsening, spinodal decomposition); others are scale invariant (self-organized criticality, roughening). Additional classes of complex patterns arise in networks with long-range interactions (rather than just spatially localized interactions) and are used for

modeling spin glasses, neural networks (Anderson and Rosenfeld 1988; Bishop 1995; Kandel, Schwartz, and Jessell 2000), or genetic networks (Kauffman 1969).

Understanding Description and Representation

The study of how we describe complex systems is itself an essential part of the study of such systems. Since science is concerned with describing reproducible phenomena and engineering is concerned with the physical realization of described functions, description is essential to both. A description is some form of identified map of the actual system onto a mathematical or linguistic object. Shannon's information theory (Shannon 1963) has taught us that the notion of description is linked to the space of possibilities. Thus, while description appears to be very concrete, any description must reflect not only what is observed but also an understanding of what might be possible to see. An important practical objective is to capture information and create representations that allow human or computer-based inquiry into the properties of the system.

Among the essential concepts relevant to the study of description is the role of universality and non-universality (Wilson 1983) as a key to the classification of systems and of their possible representations. In this context, effective studies are those that identify the class of models that can capture properties of a system, rather than those of a single model of a system. Related to this issue is the problem of testability of representations through validating the mapping of the system to the representation. Finally, the practical objective of achieving human-usable representations must contend with the finite complexity of a human being, as well as other human factors due to both "intrinsic" properties of complex human function and "extrinsic" properties that are due to the specific environment in which human beings have developed their sensory and information processing systems.

The issue of human factors can be understood more generally as part of the problem of identifying the observer's role in description. A key issue is identifying the scale of observation: the level of detail that can be seen by an observer, or the degree of distinction between possibilities (NIGMS 2002; Bar-Yam 1997). Effective descriptions have a consistent precision so that all necessary but not a lot of unnecessary information is used, irrelevant details are eliminated, and all relevant details are included. A multiscale approach (Bar-Yam 1997) relates the notion of scale to the properties of the system and relates descriptions at different scales.

The key engineering challenge is to relate the characteristics of a description to function. This involves relating the space of possibilities of the system to the space of possibilities of the environment (variety, adaptive function). Complexity is a logarithmic measure of the number of possibilities of the system, equivalently the length of the description of a state. The Law of Requisite Variety (Ashby 1957) limits the possible functions of a system of a particular complexity.

Understanding Evolutionary Dynamics

The formation of complex systems and the structural/functional change of such systems is the process of adaptation. Evolution (Darwin 1859) is the adaptation of populations through intergenerational changes in the composition of the population (the individuals of which it is formed), and learning is a similar process of adaptation of a system through changes in its internal patterns, including (but not exclusively) the changes in its component parts.

Characterizing the mechanism and process of adaptation, both evolution and learning, is a central part of complex systems research (Holland 1992; Kauffman 1993; Goodwin 1994; Kauffman 1995; Holland 1995). This research generalizes the problem of biological evolution by recognizing the relevance of processes of incremental change to the formation of all complex systems. It is diametrically opposed to the notion of creation in engineering that typically assumes new systems are invented without precursor. The reality of incremental changes in processes of creativity and design reflect the general applicability of evolutionary concepts to all complex systems.

The conventional notion of evolution of a population based upon replication with variation and selection with competition continues to be central. However, additional concepts have become recognized as important and are the subject of ongoing research, including the concepts of co-evolution (Kauffman 1993), ecosystems (Kauffman 1993), multiple niches, hierarchical or multilevel selection (Brandon and Burian 1984; Bar-Yam 2000), and spatial populations (Sayama, Kauffman, and Bar-Yam 2000). Ongoing areas of research include the traditional philosophical paradoxes involving selfishness and altruism (Sober and Wilson 1999), competition and cooperation (Axelrod 1984), and nature and nurture (Lewontin 20001). Another key area of ongoing inquiry is the origin of organization, including the origins of life (Day 1984), which investigate the initial processes that give rise to the evolutionary process of complex systems.

The engineering applications of evolutionary process are often mostly associated with the concept of evolutionary programming or genetic algorithms (Holland 1992; Fogel, Owens, and Walsh 1966). In this context, evolution is embodied in a computer. Among the other examples of the incorporation of evolution into engineering are the use of artificial selection and replication in molecular drug design (Herschlag and Cech 1990; Beaudry and Joyce 1992; Szostak 1999), and the human-induced variation with electronic replication of computer viruses, worms, and Trojan horses in Internet attacks (Goldberg et al. 1998). The importance of a wider application of evolution in management and engineering is becoming apparent. The essential concept is that evolutionary processes may enable us to form systems that are more complex than we can understand but that will still serve the functions we need. When high complexity is necessary for desired function, the system should be designed for evolvability: e.g., smaller components (subdivided modular systems) evolve faster (Simon 1998). We note, however, that in addition to the usual concept of modularity, evolution should be understood to use patterns, not elements, as building blocks. The reason for this is that patterns are more directly related to collective system function and are therefore testable in a system context.

Understanding Choices and Anticipated Effects: Games and Agents

Game theory (von Neumann and Morgenstern 1944; Smith 1982; Fudenberg and Tirole 1991; Aumann and Hart 1992) explores the relationship between individual and collective action using models where there is a clear statement of consequences (individual payoffs), that depend on the actions of more than one individual. A paradigmatic game is the “prisoner’s dilemma.” Traditionally, game theory is based upon logical agents that make optimal decisions with full knowledge of the possible outcomes, though these assumptions can be usefully relaxed. Underlying game theory is the study of the role of anticipated effects on actions and the paradoxes that

arise because of contingent anticipation by multiple anticipating agents, leading to choices that are undetermined within the narrow definition of the game and thus are sensitive to additional properties of the system. Game theory is relevant to fundamental studies of various aspects of collective behavior: altruism and selfishness, for example, and cooperation and competition. It is relevant to our understanding of biological evolution, socio-economic systems, and societies of electronic agents. At some point in the increasing complexity of games and agents, the models become agent-based models directed at understanding specific systems.

Understanding Generic Architectures

The concept of a network as capturing aspects of the connectivity, accessibility, or relatedness of components in a complex system is widely recognized as important to understanding aspects of these systems — so much so that many names of complex systems include the term "network." Among the systems that have been identified thus are artificial and natural transportation networks (roads, railroads, waterways, airways) (Maritan et al. 1996; Banavar, Maritan, and Rinaldo 1999; Dodds and Rothman 2000), social networks (Wasserman and Faust 1994), military forces (INSS 1997), the Internet (Cheswick and Burch n.d.; Zegura, Calvert, and Donahoo 1997), the World Wide Web (Lawrence and Giles 1999; Huberman et al. 1998; Huberman and Lukose 1997), biochemical networks (Service 1999; Normile 1999; Weng, Bhalla, and Iyengar 1999), neural networks (Anderson and Rosenfeld 1988; Bishop 1995; Kandel, Schwartz, and Jessell 2000), and food webs (Williams and Martinez 2000). Networks are anchored by topological information about nodes and links, with additional information that can include nodal locations and state variables, link distances, capacities, and state variables, and possibly detailed local functional relationships involved in network behaviors.

In recent years, there has been significant interest in understanding the role played by the abstract topological structure of networks represented solely by nodes and links (Milgram 1967; Milgram 1992; Watts and Strogatz 1998; Barthélémy and Amaral 1999; Watts 1999; Latora and Marchiori 2001; Barabási and Albert 1999; Albert, Jeong, and Barabási 1999; Huberman and Adamic 1999; Albert, Jeong, and Barabási 2000; Jeong et al. 2001). This work has focused on understanding the possible relationships between classes of topological networks and their functional capacities. Among the classes of networks contrasted recently are locally connected, random, small-world (Milgram 1967, 1992; Watts and Strogatz 1998; Barthélémy and Amaral 1999; Watts 1999), and scale-free networks (Latora and Marchiori 2001; Barabási and Albert 1999; Albert, Jeong, and Barabási 1999; Huberman and Adamic 1999; Albert, Jeong, and Barabási 2000; Jeong et al. 2001). Other network architectures include regular lattices, trees, and hierarchically decomposable networks (Simon 1998). Among the issues of functional capacity are which networks are optimal by some measure, e.g., their efficiency in inducing connectivity, and the robustness or sensitivity of their properties to local or random failure or directed attack. The significance of these studies from an engineering perspective is in answering such questions as, What kind of organizational structure is needed to perform what function with what level of reliability? and What are the tradeoffs that are made in different network architectures? Determining the organizational structures and their tradeoffs is relevant to all scales and areas of the

converging technologies: nanotechnology, biomedical, information, cognition, and social networks.

Understanding (Recognizing) the Paradoxes of Complex Systems

The study of complex systems often reveals difficulties with concepts that are used in the study of simpler systems. Among these are conceptual paradoxes. Many of the paradoxes take the form of the coexistence of properties that, in simpler contexts, appear to be incompatible. In some cases it has been argued that there is a specific balance of properties; for example, the "edge-of-chaos" concept suggests a specific balance of order and chaos. However, in complex systems, order and chaos often coexist, and this is only one example of the wealth of paradoxes that are present. A more complete list would include paired properties such as the following:

- Stable and adaptable
- Reliable and controllable
- Persistent and dynamic
- Deterministic and chaotic
- Random and predictable
- Ordered and disordered
- Cooperative and competitive
- Selfish and altruistic
- Logical and paradoxical
- Averaging and non-averaging
- Universal and unique

While these pairs describe paradoxes of properties, the most direct paradox in complex systems is a recognition that more than one "cause" can exist, so that A causes B, and C causes B are not mutually incompatible statements. The key to understanding paradox in complex systems is to broaden our ability to conceive of the diversity of possibilities, both for our understanding of science and for our ability to design engineered systems that serve specific functions and have distinct design tradeoffs that do not fit within conventional perspectives.

Developing Systematic Methodologies for the Study of Complex Systems

While there exists a conventional "scientific method," the study of complex systems suggests that many more detailed aspects of scientific inquiry can be formalized. The existence of a unified understanding of patterns, description, and evolution as relevant to the study of complex systems suggests that we adopt a more systematic approach to scientific inquiry. Components of such a systematic approach would include experimental, theoretical, modeling, simulation, and analysis strategies. Among the aspects of a systematic strategy are the capture of quantitative descriptions of structure and dynamics, network analysis, dynamic response, information flow, multiscale decomposition, identification of modeling universality class, and refinement of modeling and simulations.

Major Application Areas of Complex Systems Research

The following should provide a sense of the integral nature of complex systems to advances in nanotechnology, biomedicine, information technology, cognitive science, and social and global systems. A level of complexity is found in their convergence.

Nanotechnology

Development of functional systems based on nanotechnological control is a major challenge beyond the creation of single elements. Indeed, the success of

nanotechnology in controlling small elements can synergize well with the study of complex systems. To understand the significance of complex systems for nanotechnology, it is helpful to consider the smallest class of biological machines, also considered the smallest complex systems — proteins (Fersht 1999). Proteins are a marvel of engineering for design and manufacture. They also have many useful qualities that are not common in artificial systems, including robustness and adaptability through selection. The process of manufacturing a protein is divided into two parts, the creation of the molecular chain and the collapse of this chain to the functional form of the protein. The first step is ideal from a manufacturing point of view, since it enables direct manufacture from the template (RNA), which is derived from the information archive (DNA), which contains encoded descriptions of the protein chain. However, the chain that is formed in manufacture is not the functional form. The protein chain "self-organizes" (sometimes with assistance from other proteins) into its functional (folded) form. By manufacturing proteins in a form that is not the functional form, key aspects of the manufacturing process can be simplified, standardized, and made efficient while allowing a large variety of functional machines to be described in a simple language. The replication of DNA provides a mechanism for creating many equivalent information archives (by exponential growth) that can be transcribed to create templates to manufacture proteins in a massively parallel way when mass production is necessary. All of these processes rely upon rapid molecular dynamics. While proteins are functionally robust in any particular function, their functions can also be changed or adapted by changing the archive, which "describes" their function, but in an indirect and non-obvious way. The rapid parallel process of creation of proteins allows adaptation of new machines through large-scale variation and selection.

A good example of this process is found in the immune system response (Perelson and Wiegel 1999; Noest 2000; Segel and Cohen 2001; Pierre et al. 1997). The immune system maintains a large number of different proteins that serve as antibodies that can attach themselves to harmful antigens. When there is an infection, the antigens that attach most effectively are replicated in large numbers, and they are also subjected to a process of accelerated evolution through mutation and selection that generates even better-suited antibodies. Since this is not the evolutionary process of organisms, it is, in a sense, an artificial evolutionary process optimized (engineered) for the purpose of creating well-adapted proteins (machines). Antibodies are released into the blood as free molecules, but they are also used as tools by cells that hold them attached to their membranes so that the cells can attach to, or "grab hold of," antigens. Finally, proteins also form complexes and are part of membranes and biochemical networks, showing how larger functional structures can be built out of simple machines. An artificial analog of the immune system's use of evolutionary dynamics is the development of ribozymes by *in vitro* selection, now being used for drug design (Herschlag and Cech 1990; Beaudry and Joyce 1992; Szostak 1999).

Proteins and ribozymes illustrate the crossover of biology and nanotechnology. They also illustrate how complex systems concepts of self-organization, description, and evolution are important to nanotechnology. Nanotechnological design and manufacturing may take advantage of the system of manufacture of proteins or other approaches may be used. Either way, the key insights into how proteins work show

the importance of understanding various forms of description (DNA); self-reproduction of the manufacturing equipment (DNA replication by polymerase chain reaction or cell replication); rapid template-based manufacture (RNA transcription to an amino-acid chain); self-organization into functional form (protein folding); and evolutionary adaptation through replication (mutation of DNA and selection of protein function) and modular construction (protein complexes). Understanding complex systems concepts thus will enable the development of practical approaches to nanotechnological design and manufacture and to adaptation to functional requirements of nanotechnological constructs.

Biomedical Systems

At the current time, the most direct large-scale application of complex systems methods is to the study of biochemical networks (gene regulatory networks, metabolic networks) that reveal the functioning of cells and the possibilities of medical intervention (Service 1999; Normile 1999; Weng, Bhalla and Iyengar 1999). The general studies of network structure described above are complementary to detailed studies of the mechanisms and function of specific biochemical systems (von Dassow et al. 2001). High-throughput data acquisition in genomics and proteomics is providing the impetus for constructing functional descriptions of biological systems (Strausberg and Austin 1999). This, however, is only the surface of the necessary applications of complex systems approaches that are intrinsic to the modern effort to understand biological organisms, their relationships to each other, and their relationship to evolutionary history. The key to a wider perspective is recognizing that the large quantities of data currently being collected are being organized into databases that reflect the data acquisition process rather than the potential use of this information. Opportunities for progress will grow dramatically when the information is organized into a form that provides a description of systems and system functions. Since cellular and multicellular organisms, including the human being, are not simply biochemical soups, this description must capture the spatiotemporal dynamics of the system as well as the biochemical network and its dynamics. In the context of describing human physiology from the molecular scale, researchers at the Oak Ridge National Laboratory working towards this goal call it the Virtual Human Project (Appleton 2000). This term has also been used to describe static images of a particular person at a particular time (NLM 2002).

The program of study of complex systems in biology requires not only the study of a particular organism (the human being) or a limited set of model organisms, as has been done in the context of genomics until now. The problem is to develop comparative studies of systems, understanding the variety that exists within a particular type of organism (e.g., among human beings) and the variety that exists across types of organisms. Ultimately, the purpose is to develop an understanding or description of the patterns of biological systems today as well as throughout the evolutionary process. The objective of understanding variety and evolution requires us to understand not just any particular biochemical system, but the space of possible biochemical systems filtered to the space of those that are found today, their general properties, their specific mechanisms, how these general properties carry across organisms, and how they are modified for different contexts. Moreover, new approaches that consider biological organisms through the relationship of

structure and function and through information flow are necessary to this understanding.

Increasing knowledge about biological systems is providing us with engineering opportunities and hazards. The great promise of our biotechnology is unrealizable without a better understanding of the systematic implications of interventions that we can do today. The frequent appearance of biotechnology in the popular press through objections to genetic engineering and cloning reveals the great specific knowledge and the limited systemic knowledge of these systems. The example of corn genetically modified for feed and its subsequent appearance in corn eaten by human beings (Quist and Chapela 2001) reveals the limited knowledge we have of indirect effects in biological systems. This is not a call to limit our efforts, simply to focus on approaches that emphasize the roles of indirect effects and explore their implications scientifically. Without such studies, not only are we shooting in the dark, but in addition we will be at the mercy of popular viewpoints.

Completion of the virtual human project would be a major advance toward creating models for medical intervention. Such models are necessary when it is impossible to test multidrug therapies or specialized therapies based upon individual genetic differences. Intervention in complex biological systems is an intricate problem. The narrow bridge that currently exists between medical double blind experiments and the large space of possible medical interventions can be greatly broadened through systemic models that reveal the functioning of cellular systems and their relationship to cellular function. While today individual medical drugs are tested statistically, the main fruit of models will be as follows:

- to reveal the relationship between the function of different chemicals and the possibility of multiple different types of interventions that can achieve similar outcomes
- the possibility of discovering small variations in treatment that can affect the system differently
- possibly most importantly, to reveal the role of variations among human beings in the difference of response to medical treatment

A key aspect of all of these is the development of complex systems representations of biological function that reveal the interdependence of biological system and function.

Indeed, the rapid development of medical technologies and the expectation of even more dramatic changes should provide an opportunity for, even require, a change in the culture of medical practice. Key to these changes should be understanding the dynamic state of health. Conventional *homeostatic* perspectives on health are being modified to *homeodynamic* perspectives (Goldberger, Rigney, and West 1990; Lipsitz and Goldberger 1992). What is needed is a better understanding of the functional capabilities of a healthy individual to respond to changes in the external and internal environment for self-repair or -regulation. This is essential to enhance the individual's ability to maintain his or her own health. For example, while physical decline is a problem associated with old age, it is known that repair and regulatory mechanisms begin to slow down earlier, e.g., in the upper 30s, when professional athletes typically end their careers. By studying the dynamic response of an individual and changes over his/her life cycle, it should be possible to

understand these early aspects of aging and to develop interventions that maintain a higher standard of health. More generally, understanding the network of regulatory and repair mechanisms should provide a better mechanism for dynamic monitoring — with biomedical sensors and imaging — health and disease and the impact of medical interventions. This would provide key information about the effectiveness of interventions for each individual, enabling feedback into the treatment process that can greatly enhance its reliability.

Information Systems

Various concepts have been advanced over the years for the importance of computers in performing large-scale computations or in replacing human beings through artificial intelligence. Today, the most apparent role of computers is as personal assistants and as communication devices and information archives for the socioeconomic network of human beings. The system of human beings and the Internet has become an integrated whole leading to a more intimately linked system. Less visibly, embedded computer systems are performing various specific functions in information processing for industrial age devices like cars. The functioning of the Internet and the possibility of future networking of embedded systems reflects the properties of the network as well as the properties of the complex demands upon it. While the Internet has some features that are designed, others are self-organizing, and the dynamic behaviors of the Internet reflect problems that may be better solved by using more concepts from complex systems that relate to interacting systems adapting in complex environments rather than conventional engineering design approaches.

Information systems that are being planned for business, government, military, medical, and other functions are currently in a schizophrenic state where it is not clear whether distributed intranets or integrated centralized databases will best suit function. While complex systems approaches generally suggest that creating centralized databases is often a poor choice in the context of complex function, the specific contexts and degree to which centralization is useful must be understood more carefully in terms of their functions and capabilities, both now and in the future (Bar-Yam 2001).

A major current priority is enabling computers to automatically configure themselves and carry out maintenance without human intervention (Horn 2001). Currently, computer networks are manually configured, and often the role of various choices in configuring them are not clear, especially for the performance of networks. Indeed, evidence indicates that network system performance can be changed dramatically using settings that are not recognized by the users or system administrators until chance brings these settings to their attention. The idea of developing more automatic processes is a small part of the more general perspective of developing adaptive information systems. This extends the concept of self-configuring and self-maintenance to endowing computer-based information systems with the ability to function effectively in diverse and variable environments. In order for this functioning to take place, information systems must, themselves be able to recognize patterns of behavior in the demands upon them and in their own activity. This is a clear direction for development of both computer networks and embedded systems.

Development of adaptive information systems in networks involves the appearance of software agents. Such agents range from computer viruses to search engines and may have communication and functional capabilities that allow social interactions among them. In the virtual world, complex systems perspectives are imperative in considering such societies of agents. As only one example, the analogy of software agents to viruses and worms has also led to an immune system perspective in the design of adaptive responses (Forrest, Hofmeyr, and Somayaji 1997; Kephart et al. 1997).

While the information system as a system is an important application of complex systems concepts, complex systems concepts also are relevant to considering the problem of developing information systems as effective repositories of information for human use. This involves two aspects, the first of which is the development of repositories that contain descriptions of complex systems that human beings would like to understand. The example of biological databases in the previous section is only one example. Other examples are socio-economic systems, global systems, and astrophysical systems. In each case, the key issue is to gain an understanding of how such complex systems can be effectively represented. The second aspect of designing such information repositories is the recognition of human factors in the development of human-computer interfaces (Norman and Draper 1986; Nielsen 1993; Hutchins 1995). This is important in developing all aspects of computer-based information systems, which are used by human beings and designed explicitly or implicitly to serve human beings.

More broadly, the networked information system that is being developed serves as part of the human socio-economic-technological system. Various parts of this system, which includes human beings and information systems, as well as the system as a whole, are functional systems. The development and design of such a self-organizing system and the role of science and technology is a clear area of application of complex systems understanding and methods. Since this is a functional system based upon a large amount of information, among the key questions is how should the system be organized when action and information are entangled.

Cognitive Systems

The decade of the 1990s was declared by President George Bush, senior (1990), the "decade of the brain," based, in part, on optimism that new experimental techniques such as Positron Emission Tomography (PET) imaging would provide a wealth of insights into the mechanisms of brain function. However, a comparison of the current experimental observations of cognitive processes with those of biochemical processes of gene expression patterns reveals the limitations that are still present in these observational techniques in studying the complex function of the brain. Indeed, it is reasonable to argue that the activity of neurons of a human being and their functional assignment is no less complex than the expression of genes of a single human cell.

Current experiments on gene expression patterns allow the possibility of knocking out individual genes to investigate the effect of each gene on the expression pattern of all other genes measured individually. The analogous capability in the context of cognitive function would be to incapacitate an individual neuron and investigate the effect on the firing patterns of all other neurons

individually. Instead, neural studies are based upon sensory stimulation and measures of the average activity of large regions of cells. In gene expression studies, many cells are used with the same genome and a controlled history through replication, and averages are taken of the behavior of these cells. In contrast, in neural studies averages are often taken of the activity patterns of many individuals with distinct genetic and environmental backgrounds. The analogous biochemical experiment would be to average behavior of many cells of different types from a human body (muscle, bone, nerve, red blood cell, etc.) and different individuals to obtain a single conclusion about the functional role of the genes.

The more precise and larger quantities of genome data have revealed the difficulties in understanding genomic function and the realization that gene function must be understood through models of genetic networks (Fuhrman et al. 1998). This is to be contrasted with the conclusions of cognitive studies that investigate the aggregate response of many individuals to large-scale sensory stimuli and infer functional assignments. Moreover, these functional assignments often have limited independently verifiable or falsifiable implications. More generally, a complex systems perspective suggests that it is necessary to recognize the limitations of the assignment of function to individual components ranging from molecules to subdivisions of the brain; the limitations of narrow perspectives on the role of environmental and contextual effects that consider functioning to be independent of effects other than the experimental stimulus; and the limitations of expectations that human differences are small and therefore that averaged observations have meaning in describing human function.

The problem of understanding brain and mind can be understood quite generally through the role of relationships between patterns in the world and patterns of neuronal activity and synaptic change. While the physical and biological structure of the system is the brain, the properties of the patterns identify the psychofunctioning of the mind. The relationship of external and internal patterns are further augmented by relationships between patterns within the brain. The functional role of patterns is achieved through the ability of internal patterns to represent both concrete and abstract entities and processes, ranging from the process of sensory-motor response to internal dialog. This complex nonlinear dynamic system has a great richness of valid statements that can be made about it, but identifying an integrated understanding of the brain/mind system cannot be captured by perspectives that limit their approach through the particular methodologies of the researchers involved. Indeed, the potential contributions of the diverse approaches to studies of brain and mind have been limited by the internal dynamics of the many-factioned scientific and engineering approaches.

The study of complex systems aspects of cognitive systems, including the description of patterns in the world and patterns in mind, the construction of descriptions of complex systems, and the limitations on information processing that are possible for complex systems are relevant to the application of cognitive studies to the understanding of human factors in man-machine systems (Norman and Draper 1986; Nielsen 1993; Hutchins 1995) and more generally to the design of systems that include both human beings and computer-based information systems as functional systems. Such hybrid systems, mentioned previously in the section on

information technology, reflect the importance of the converging technology approach.

The opportunity for progress in understanding the function of the networked, distributed neuro-physiological system also opens the possibility of greater understanding of development, learning, and aging (NIMH n.d.; Stern and Carstensen 2000; Mandell and Schlesinger 1990; Davidson, Teicher, and Bar-Yam 1997). While the current policy of education reform is using a uniform measure of accomplishment and development through standardized testing, it is clear that more effective measures must be based on a better understanding of cognitive development and individual differences. The importance of gaining such knowledge is high because evaluation of the effectiveness of new approaches to education typically requires a generation to see the impact of large-scale educational changes on society. The positive or negative effects of finer-scale changes appear to be largely inaccessible to current research. Thus, we see the direct connection between complex systems approaches to cognitive science and societal policy in addressing the key challenge of the education system. This in turn is linked to the solution of many other complex societal problems, including poverty, drugs, and crime, and also to effective functioning of our complex economic system requiring individuals with diverse and highly specialized capabilities.

Studies of the process of aging are also revealing the key role of environment in the retention of effective cognitive function (Stern and Carstensen 2000; Mandell and Schlesinger 1990; Davidson, Teicher, and Bar-Yam 1997). The notion of "use it or lose it," similar to the role of muscular exercise, suggests that unused capabilities are lost more rapidly than used ones. While this is clearly a simplification, since losses are not uniform across all types of capabilities and overuse can also cause deterioration, it is a helpful guideline that must be expanded upon in future research. This suggests that research should focus on the effects of the physical and social environments for the elderly and the challenges that they are presented with.

We can unify and summarize the complex systems discussion of the cognitive role of the environment for children, adults, and the elderly by noting that the complexity of the environment and the individual must be matched for effective functioning. If the environment is too complex, confusion and failure result; if the environment is too simple, deterioration of functional capability results. One approach to visualizing this process is to consider that the internal physical parts and patterns of activity are undergoing evolutionary selection dictated by the patterns of activity that result from environmental stimulation. This evolutionary approach also is relevant to the recognition that individual differences are analogous to different ecological niches. A more detailed research effort would not only consider the role of complexity but also the effect of specific patterns of environment and patterns of internal functioning, individual differences in child development, aging, adult functioning in teams, and hybrid human-computer systems.

Social Systems and Societal Challenges

While social systems are highly complex, there are still relatively simple collective behaviors that are not well understood. These include commercial fads, market cycles and panics, bubbles and busts. Understanding the fluctuating dynamics and predictability of markets continues to be a major challenge. It is

important to emphasize that complex systems studies are not necessarily about predicting the market, but about understanding its predictability or lack thereof.

More generally, there are many complex social challenges associated with complex social systems ranging from military challenges to school and education system failures, healthcare errors, and problems with quality of service. Moreover, other major challenges remain in our inability to address fundamental social ills such as poverty (in both developed and undeveloped countries), drug use, and crime. To clarify some aspects of social systems from a complex systems perspective, it is helpful to focus on one of these, and the current military context is a convenient focal point.

Wars are major challenges to our national abilities. The current war on terrorism is no exception. In dealing with this challenge, our leadership, including the president and the military, has recognized that this conflict is highly complex. Instead of just sending in tens to hundreds of thousands of troops, as was done in the Gulf War, there is a strategy of using small teams of special forces to gain intelligence and lay the groundwork for carefully targeted, limited, and necessary force.

A large-scale challenge can be met by many individuals doing the same thing at the same time or by repeating the same action, similar to a large military force. In contrast, a complex challenge must be met by many individuals doing many different things at different times. Each action has to directly match the local task that must be done. The jungles of Vietnam and the mountains of Afghanistan, reported to have high mountains and deep narrow valleys, are case studies in complex terrains. War is complex when targets are hidden, not only in the terrain but also among people — bystanders or friends. It is also complex when the enemy can itself do many different things, when the targets are diverse, the actions that must be taken are specific, and the difference between right and wrong action is subtle.

While we are still focused on the war on terrorism, it seems worthwhile to transfer the lessons learned from different kinds of military conflicts to other areas where we are trying to solve major problems. Over the past 20 years, the notion of war has been used to describe the War on Poverty, the War on Drugs, and other national challenges. These were called wars because they were believed to be challenges requiring the large force of old-style wars. They are not. They are complex challenges that require detailed intelligence and the application of the necessary forces in the right places. Allocating large budgets for the War on Poverty did not eliminate the problem; neither does neglect. The War on Drugs has taken a few turns, but even the recent social campaign “Just say no!” is a large-scale approach. Despite positive intentions, we have not won these wars because we are using the wrong strategy.

There are other complex challenges that we have dealt with using large forces. Third World development is the international version of the War on Poverty to which the World Bank and other organizations have applied large forces. Recently, more thoughtful approaches are being taken, but they have not gone far enough. There is a tendency to fall into the “central planning trap.” When challenges become complex enough, even the very notion of central planning and control fails. Building functioning socioeconomic systems around the world is such a complex

problem that it will require many people taking small and targeted steps — like the special forces in Afghanistan.

There are other challenges that we have not yet labeled wars, which are also suffering from the same large-force approach. Among these are cost containment in the medical system and improving the education system. In the medical system, the practice of cost controls through managed care is a large-force approach that started in the early 1980s. Today, the medical system quality of care is disintegrating under the stresses and turbulence generated by this strategy. Medical treatment is clearly one of the most complex tasks we are regularly engaged in. Across-the-board cost control should not be expected to work. We are just beginning to apply the same kind of large-scale strategy to the education system through standardized testing. Here again, a complex systems perspective suggests that the outcomes will not be as positive as the intentions.

The wide applicability of lessons learned from fighting complex wars and the effective strategies that resulted should be further understood through research projects that can better articulate the relevant lessons and how they pertain to solving the many and diverse complex social problems we face.

Global and Larger Systems

Global systems — physical, biological, and social — are potentially the most complex systems studied by science today. Complex systems methods can provide tools for analyzing their large-scale behavior. Geophysical and geobiological systems, including meteorology, plate tectonics and earthquakes, river and drainage networks, the biosphere and ecology, have been the motivation for and the application of complex systems methods and approaches (Dodds and Rothman 2000; Lorenz 1963; Bak and Tang 1989; Rundle, Turcotte, and Klein 1996; NOAA 2002). Such applications also extend to other planetary, solar, and astrophysical systems. Converging technologies to improve human performance may benefit from these previous case studies.

Among the key problems in studies of global systems is understanding the indirect effects of global human activity, which in many ways has reached the scale of the entire earth and biosphere. The possibility of human impact on global systems through overexploitation or other by-products of industrial activity has become a growing socio-political concern. Of particular concern is the impact of human activity on the global climate (climate change and global warming) and on the self-sustaining properties of the biosphere through exploitation and depletion of key resources (e.g., food resources like fish, energy resources like petroleum, deforestation, loss of biodiversity). Other global systems include global societal problems that can include the possibility of global economic fluctuations, societal collapse, and terrorism. Our effectiveness in addressing these questions will require greater levels of understanding and representations of indirect effects, as well as knowledge of effective mechanisms for intervention, if necessary. In this context, the objective is to determine which aspects of a system can be understood or predicted based upon available information, along with the level of uncertainty in such predictions. In some cases, the determination of risk or uncertainty is as important as the prediction of the expected outcome. Indeed, knowing “what is the worst that can happen” is often an important starting point for effective decision-making.

In general, the ability of humanity to address global problems depends on the collective behavior of people around the world. Global action is now typical in response to local natural disasters (earthquakes, floods, volcanoes, droughts); man-made problems from wars (Gulf War, Bosnia, Rwanda, the war on terrorism); and environmental concerns (international agreements on environment and development). In addition, there is a different sense in which addressing global concerns requires the participation of many individuals: The high complexity of these problems implies that many individuals must be involved in addressing these problems, and they must be highly diverse and yet coordinated. Thus, the development of complex systems using convergent technologies that facilitate human productivity and cooperative human functioning will be necessary to meet these challenges.

What is to be Done?

The outline above of major areas of complex systems research and applications provides a broad view in which many specific projects should be pursued. We can, however, single out three tasks that, because of their importance or scope, are worth identifying as priorities for the upcoming years: (1) transform education; (2) develop sets of key system descriptions; and (3) design highly complex engineering projects as evolutionary systems.

Transform Education

The importance of education in complex systems concepts for all areas of science, technology, and society at large has been mentioned above but should be reemphasized. There is need for educational materials and programs that convey complex systems concepts and methods and are accessible to a wide range of individuals, as well as more specific materials and courses that explain their application in particular contexts. A major existing project on fractals can be used as an example (Buldyrev et al. n.d.). There are two compelling reasons for the importance of such projects. The first is the wide applicability of complex systems concepts in science, engineering, medicine, and management. The second is the great opportunity for engaging the public in exciting science with a natural relevance to daily life and enhancing their support for ongoing and future research. Ultimately, the objective is to integrate complex systems concepts throughout the educational system.

Develop Sets of Key System Descriptions

There are various projects for describing specific complex systems (NOAA 2002; Kalra et al. 1988; Goto, Kshirsagar, and Magnenat-Thalmann 2001; Heudin 1999; Schaff et al. 1997; Tomita et al. 1999), ranging from the earth to a single cell, which have been making substantial progress. Some of these focus more on generative simulation, others on representation of observational data. The greatest challenge is to merge these approaches and develop system descriptions that identify both the limits of observational and modeling strategies and the opportunities they provide jointly for the description of complex systems. From this perspective, some of the most exciting advances are in representation of human forms in computer-based animation (Kalra et al. 1988; Goto, Kshirsagar, and Magnenat-Thalmann 2001; Heudin 1999), and particularly, in projecting human beings electronically. Pattern

recognition is performed on realtime video to obtain key information about dynamic facial expression and speech, which is transmitted electronically to enable animation of a realistic computer-generated image that represents, in real time, the facial expression and speech of the person at a remote location (Goto, Kshirsagar, and Magnenat-Thalmann 2001). Improvement in such systems is measured by the growing bandwidth necessary for the transmission, which reflects our inability to anticipate system behavior from prior information.

To advance this objective more broadly, developments in systematic approaches (including quantitative languages, multiscale representations, information capture, and visual interfaces) are necessary, in conjunction with a set of related complex systems models. For example, current computer-based tools are largely limited to separated procedural languages (broadly defined) and databases. A more effective approach may be to develop quantitative descriptive languages based on lexical databases that merge the strength of human language for description with computer capabilities for manipulating and visually representing quantitative attributes (Smith, Bar-Yam, and Gelbart 2001). Such extensible quantitative languages are a natural bridge between quantitative mathematics, physics, and engineering languages and qualitative lexicons that dominate description in biology, psychology, and social sciences. They would facilitate describing structure, dynamics, relationships, and functions better than, for example, graphical extensions of procedural languages. This and other core complex systems approaches should be used in the description of a set of key complex systems under a coordinating umbrella.

For each system, an intensive collection of information would feed a system representation whose development would be the subject and outcome of the project. For example, in order to develop a representation of a human being, there must be intensive collection of bio-psycho-social information about the person. This could include multisensor monitoring of the person's physical (motion), psycho-social (speech, eye-motion), physiological (heart rate), and biochemical (food and waste composition, blood chemistry) activity over a long period of time, with additional periodic biological imaging and psychological testing. Virtual world animation would be used to represent both the person and his/her environment. Models of biological and psychological function representing behavioral patterns would be incorporated and evaluated. Detailed studies of a particular individual along with comparative studies of several individuals would be made to determine both what is common and what is different. As novel relevant convergent technologies become available that would affect human performance or affect our ability to model human behavior, they can be incorporated into this study and evaluated. Similar coordinating projects would animate representations of the earth, life on earth, human civilization, a city, an animal's developing embryo, a cell, and an engineered system, as suggested above. Each such project is both a practical application and a direct test of the limits of our insight, knowledge, and capabilities. Success of the projects is guaranteed because their ultimate objective is to inform us about these limits.

Design Highly Complex Engineering Projects as Evolutionary Systems

The dramatic failures in large-scale engineering projects such as the Advanced Automation System (AAS), which was originally planned to modernize air traffic control, should be addressed by complex systems research. The AAS is possibly the

largest engineering project to be abandoned. It is estimated that several billion dollars were spent on this project. Moreover, cost overruns and delays in modernization continue in sequel projects. One approach to solving this problem, simplifying the task definition, cannot serve when the task is truly complex, as it appears to be in this context. Instead, a major experiment should be carried out to evaluate implementation of an evolutionary strategy for large-scale engineering. In this approach, the actual air traffic control system would become an evolving system, including all elements of the system, hardware, software, the air traffic controllers, and the designers and manufacturers of the software and hardware. The system context would be changed to enable incremental changes in various parts of the system and an evolutionary perspective on population change.

The major obstacle to any change in the air traffic control system is the concern for safety of airplanes and passengers, since the existing system, while not ideally functioning, is well tested. The key to enabling change in this system is to introduce redundancy that enables security while allowing change. For example, in the central case of changes in the air traffic control stations, the evolutionary process would use "trainers" that consist of doubled air traffic control stations, where one has override capability over the other. In this case, rather than an experienced and inexperienced controller, the two stations are formed of a conventional and a modified station. The modified station can incorporate changes in software or hardware. Testing can go on as part of operations, without creating undue risks. With a large number of trainers, various tests can be performed simultaneously and for a large number of conditions. As a particular system modification becomes more extensively tested and is found to be both effective and reliable, it can be propagated to other trainers, even though testing would continue for extended periods of time. While the cost of populating multiple trainers would appear to be high, the alternatives have already been demonstrated to be both expensive and unsuccessful. The analogy with paired chromosomes in DNA can be seen to reflect the same design principle of redundancy and robustness. These brief paragraphs are not sufficient to explain the full evolutionary context, but they do resolve the key issue of safety and point out the opening that this provides for change. Such evolutionary processes are also being considered for guiding other large-scale engineering modernization programs (Bar-Yam 2001).

Conclusions

The excitement that is currently felt in the study of complex systems arises not from a complete set of answers but rather from the appearance of a new set of questions, which are relevant to NBIC. These questions differ from the conventional approaches to science and technology and provide an opportunity to make major advances in our understanding and in applications.

The importance of complex systems ideas in technology begins through recognition that novel technologies promise to enable us to create ever more complex systems. Even graphics-oriented languages like OpenGL are based on a procedural approach to drawing objects rather than representing them. Moreover, the conventional boundary between technology and the human beings that use them is not a useful approach to thinking about complex systems of human beings and technology. For example, computers as computational tools have given way to

information technology as an active interface between human beings that are working in collaboration. This is now changing again to the recognition that human beings and information technology are working together as an integrated system.

More generally, a complex systems framework provides a way in which we can understand how the planning, design, engineering, and control over simple systems gives way to new approaches that enable such systems to arise and be understood with limited or indirect planning or control. Moreover, it provides a way to better understand and intervene (using technology) in complex biological and social systems.

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MIND OVER MATTER IN AN ERA OF CONVERGENT TECHNOLOGIES

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Within the next 10 to 15 years, economically viable activities connected with nanoscience, bioscience, information technology, and cognitive science (NBIC) will have interlaced themselves within ongoing successful technologies, resulting in new and improved commercial endeavors. The impact of such eventualities would be enormous even if the emerging activities were developing independently, but with a range of synergies, their overlapping emergence and transitioning into the applied engineering arena promises to result in industrial products and technologies that stretch our imaginations to the point that they appear fanciful. Indeed, it is becoming more widely acknowledged that the potential of the new convergent NBIC technologies for influencing and defining the future is unlimited and likely unimaginable.

Nevertheless, leading personalities and recognized experts have attempted to gaze into the future to look at the character of the emerging technologies. What they herald are enterprises that dramatically impact mankind's physical environment, commerce, and, indeed, the performance of the human species itself. Intellectual leaders have divined some of the very likely near-term outcomes that will help determine the technologies that flourish beyond the 10-15 year timeframe. Examples of products of such technologies have ranged over the full panoply of futuristic outcomes, from unbelievably fast nanoprocessors to the creation of nanobots. Even more resolution to what we can anticipate is being provided in various forums associated with the present workshop focusing on NBIC technologies.

However, the emerging NBIC technologies — figuratively speaking, our starships into our future — will only take us as far as the skills of those who captain and chart the various courses. But acquisition of skills depends on many things, including most assuredly the existence of a positive social environment that allows creative juices to flow. As a result, educational issues, both *pedagogy* and *people*, surface as ingredients fundamental to the realization of successful technologies.

Pedagogy

It seems clear that progress in the NBIC arena will necessitate contributions from several fields whose practitioners have tended to address problems in a sequential manner. The operative approach has been as follows: first something useful is found; then, if providence allows it, someone else gets involved with new insights or new capabilities; ultimately, commercial products are realized. In this era of convergent technologies, such a recipe can no longer be accepted, and practitioners must be taught in a new way.

The new pedagogy involves multidisciplinary training at the intersection of traditional fields, and it involves scientists, engineers, and social scientists. Although we still will need the ivory tower thinker, we will especially need to engage the intellects of students and established researchers in multidisciplinary, multi-investigator pursuits that lead to different ways of looking at research findings as well as to use different research tools. In acknowledgement of the necessity for multidiscipline skills and the participation in cross-discipline collaborations, nearly all of the funding agencies and private foundations provide substantial funding for

research as well as for education of students in projects that are multidisciplinary and cross-disciplinary in character. A case in point is the Integrative Graduate Education and Research Training (IGERT) project (established by NSF in 1999), housed at The City University of New York, which involves three colleges from CUNY (the City College, Hunter College, and the College of Staten Island); Columbia University; and the University of Rochester.

IGERT participants are dedicated to the creation of research initiatives that span disciplinary and institutional boundaries and to the objective that such initiatives be reflected in the education and training of all its students. The overall goal is to educate and train the next generation of scientists in an interdisciplinary environment whereby a graduate student may participate in all the phases of a research project: synthesis, materials fabrication, and characterization. Our students, though trained as described, will be rigorously educated in a field of chemistry, engineering, or materials science. It is expected that such students will develop imaginative problem-solving skills and acquire a broad range of expertise and fresh, interdisciplinary outlooks to use in their subsequent positions. Our students will not just be sources of samples or instrument technicians but full partners with multidisciplinary training.

Without dealing with the specific science focus, the value-added elements of the CUNY-IGERT are described below:

- Multidisciplinary training (with choice of home institution after initial matriculation period at CUNY)
- IGERT-focused seminar program (via video-teleconferencing)
- Reciprocal attendance at annual symposia
- Expanded training opportunities (rotations and extended visits to appropriate collaborating laboratories)
- Formalized special courses (utilizing distance learning technology)
- Credit-bearing enrichment activities and courses
- Collaborative involvement with industry and national laboratories
- International partnerships that provide a global perspective in the research and educational exposures of students

Such a model for coupling research and education will produce individuals capable of creatively participating in the NBIC arena.

The People

The second key educational issue concerns the people who make the science and engineering advances that will form the bedrock of new technologies. If these individuals are not equitably drawn from the populace at large, then one can predict with certitude that social equity and displacement issues will gain momentum with every advance and can, in fact, dissipate or forestall the anticipated benefits of any endeavor.

It is thus clearly in America's best interest to ensure equitable participation of all elements in the front-line decision-making circles, in particular, to include groups that are historically underrepresented in leading-edge science and engineering during this era of anticipated, unbridled growth of NBIC technologies. The rich opportunities to make contributions will help members of underrepresented groups,

especially, to reassert and revalidate their forgotten and sometimes ignored historical science and technological prowess. Success here would go a long way to avoid an enormous challenge to a bright future. What we stand to gain is the inclusion of the psychology and intellectual talents of an important segment of our society in solutions of ongoing and future world-shaping events. Two important activities immediately come to mind that make the point. One represents an opportunity lost; the second, a challenge we dare not ignore.

The first was NASA's space-venturing time capsule to other worlds several decades ago. Among many good things associated with this undertaking was one I consider unfortunate, a single-race representation of the inhabitants of the Earth. Clearly, a different psychological view, one more inclusive, should have prevailed and probably would have if minorities had had a say.

The second is the mapping of the human genome. The resultant data bank, I should think, will reflect the proclivities and prejudices of its creators, and its exploitation in the battle against genetic diseases. Clearly we should all have a hand in what it looks like and how it is to be used.

Summary

Only by utilizing new educational approaches for providing NBIC practitioners with the skills and insights requisite for success and also by making sure that historically underrepresented citizens are not left behind can the full promise of this era of convergence be realized.

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CONVERGING TECHNOLOGY AND EDUCATION FOR IMPROVING HUMAN PERFORMANCE

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This statement will address two general issues. One relates to potential uses for nanotechnology in neuroscience and biomedical engineering. The other addresses suggested issues in the education of potential scientists who will be most effective in the development of the new technologies.

Potential Uses for Nanotechnology in Neuroscience Research and Biomedical Engineering

The following areas have the highest potential for application:

a) Basic Neuroscience

- Exploration of single neurons (see Zygmond et al. 1999, a graduate-level reference for the concepts presented below):
  - Develop nanoscale delivery systems for compounds relevant to the nervous system such as neurotransmitters or receptor blockers, etc.

These would be used for distributed application to single cells in culture and *in situ*.

- Develop nanoscale sensors, conductive fibers for stimulating and recording the electrical activity from the surface of single neurons.
- Combine delivery and sensing nanofibers with exploration of single neurons in culture, both soma and dendrites, both spread over surface of neuron

b) Observation and Study of Growing Cells

- Use sensors and delivery systems to study neuronal development or regenerating fibers *in situ.* This requires that nanosensors and nano-optical devices be placed in a developing or injured nervous system, either alone or in combination with MEMS or aVLSI devices

c) Development

- Monitor growth cones with nano-optical devices
- Provide growth factors with nanoscale delivery systems

d) Regeneration

- Study processes as neurons are attempting or failing to regenerate. How do neurons behave as they try to grow? What happens as they encounter obstacles or receptors?

e) Applications in Biomedical Engineering

The following applications assume that nanofibers can be grown or extruded from the tips of microwires *in situ:*

- Monitor spinal cord injury or brain injury
  - use nanofibers to assess the local levels of calcium in injury sites
  - use nano delivery systems to provide local steroids to prevent further damage
- Neuroprosthetic devices
  - Use nanofibers in conjunction with MEMS or aVLSI devices as delivery systems and stimulating devices for neuroprosthetic devices — make them more efficient.
  - Use CPG prosthetic device in conjunction with microwires to stimulate locomotion
  - Develop artificial cochlea with more outputs
  - Develop artificial retina with more complex sensors – in combination with aVLSI retinas

Figure F.2 illustrates the positioning of a cochlear implant in the human cochlea (Zygmond et al. 1999). These devices are in current use. The electrode array is inserted through the round window of the cochlea into the fluid-filled space called *scala tympani*. It likely stimulates the peripheral axons of the primary auditory neurons, which carry messages via the auditory nerve into the brain. It is presently known that the information encoded by the sparsely distributed electrodes is

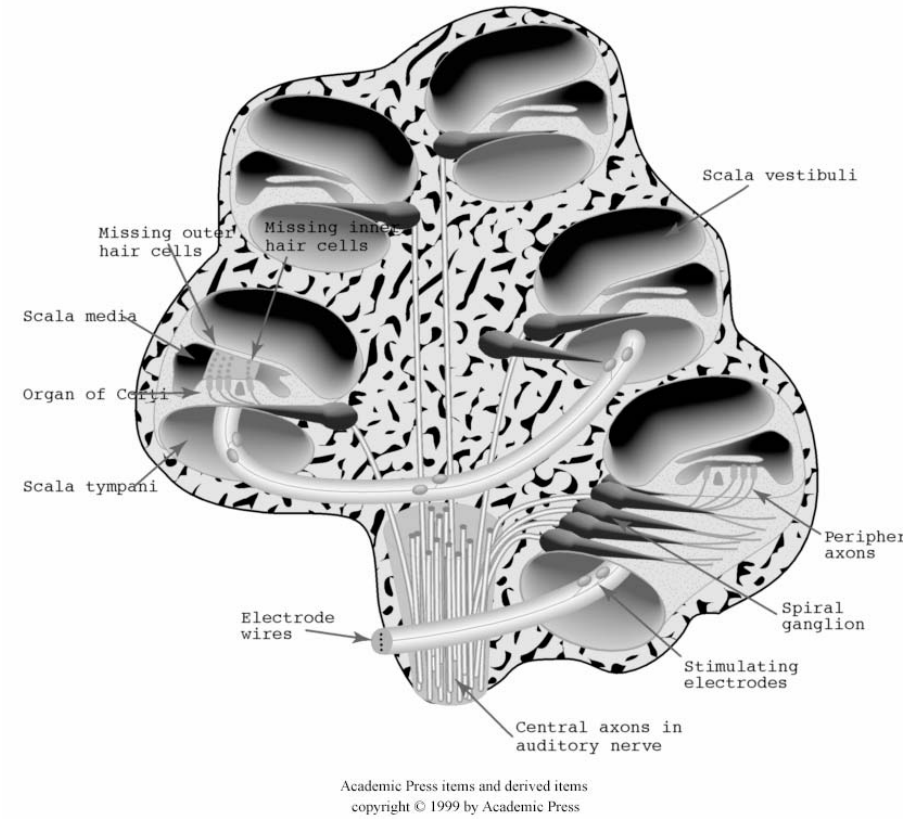

Figure F.2. The positioning of a cochlear implant in the human cochlea.

nowhere near that carried by the human cochlea. The device, therefore, is of limited value for hearing-impaired individuals with long-term auditory nerve damage that predates their normal speech learning (Moller 2001). If nanofibers could be deployed from each electrode to better distribute the information, it would likely improve the quality of the device considerably. This would be a relative easy use of the new technology, with easy testing to affirm its usefulness.

Training the Future Developers of Nanotechnology

In the new era of converging technologies, one can become either a generalist and be superficially capable in many fields, or one can become a specialist and master a single field. If one chooses the former route, one is unlikely to produce deep, insightful work. If one chooses the latter route, then it is only possible to take full advantage of the convergence of the technologies by working in collaboration with others who are expert in the other relevant fields. Unfortunately, our present educational system does not foster the type of individual who works well in collaborations.

To achieve the training of good scientists who have the capacity to work well in multidisciplinary groups, there are several new kinds of traits necessary. The first

and perhaps most difficult is to learn to communicate across the disciplines. We learn the technical language of our respective disciplines and use it to convey our thoughts as clearly and precisely as possible. However, researchers in other disciplines are unfamiliar with the most technical language we prefer to use. When talking across the bridges we seek to build, we must learn to translate accurately but clearly to intelligent listeners who will not know our respective languages. We must begin to train our students to learn the skill of communicating across the disciplinary divides. We must develop programs in which students are systematically called upon to explain their work or the work of others to their peers in other areas. Thus, the best programs will be those that throw the students from diverse disciplines together. Narrowly focused programs may turn out neuroscientists superbly trained for some functions, but they will not be good at collaborative efforts with scientists in other fields without considerable additional work. They will not easily produce the next generation of researcher who successfully forms collaborative efforts to use the new converging technologies.

We should also begin to systematically pose challenges to our students such that they must work in teams of mixed skills, teams of engineers, mathematicians, biologists, chemists, and cognitive scientists. This will provide the flavor of the span that will be required. We cannot train our students to be expert in this broad a range of fields; therefore, we must train and encourage them to communicate across the range and to seek out and work with experts who offer the expertise that will allow the best science to be done. Funding agencies must continue to enlarge the mechanisms that support this type of work if they want to have a unique position in fostering the development and optimal utilization of the new technologies as applied to neuroscience, among other fields.

My experience with the Telluride Workshop on Neuromorphic Engineering has given me some important insights into the optimal methods for educating for the future. It has shown me that it will be easier to train engineers to understand biology, than to train biologists to comprehend engineering. There are some notable exceptions, fortunately, like Miguel Nicolelis and Rodolfo Llinás. Among biologists, there is beginning to be curiosity and enthusiasm for engineering, robotics, and the new emerging technologies. This must be fostered through showcasing technological accomplishments such as successful robotic efforts and the analog VLSI retinas and cochleas developed using neuromorphic engineering. We must also try harder to get biologists to attend the Telluride Workshop and to stay long enough to gain some insights into the power of the approach. The field of nanobiotechnology is growing much faster among engineers than among biologists. We must work harder to improve our outreach to biologists.

The formation of workshops such as Telluride is a good way to begin to put together the necessary groups for the exploitation of the new methods being developed in nanotechnology. It is likely that the full potential for nanodevices will only be reached by uniting engineers with biologists. Biologists presently have little exposure to information about nanotechnology. Comparatively, the engineers know relatively little about the real neuronal substrate with which they seek to interface. It will not be a trivial task to actually understand what will emerge when nanotubes are directly contacting neurons, stimulating them, and recording from them. It will require considerable expertise and imagination. Exposing biologists to the potential

power and usefulness of the technology, and exposing engineers to the complexity of the biological substrate, can only come about through intense interactions; it cannot come about through groups operating alone. The journal *Science* has done a great deal to bring nanotechnology to the attention of the general scientist. However, no true understanding can come without hard work.

Development of novel bioengineering programs will be another approach to development of nanotechnology. Training biologists and engineers in the same educational program will go a long way to overcoming some of the present ignorance. Nanotechnology is difficult. The underlying chemistry and physics will not come easily to everyone. It is most likely that the best method of developing it is through explicit programmatic efforts to build collaborative teams of engineers and biologists. Summer workshops can provide incentives by exposing individuals to the potentials of the union, but only through full-fledged educational programs can the efforts move forward effectively.

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VISIONARY PROJECTS

CONVERGING TECHNOLOGIES: A K-12 EDUCATION VISION

James G. Batterson and Alan T. Pope, NASA Langley Research Center

Over the next 15 years, converging technologies (CT), the synergistic interplay of nano-, bio-, information, and cognitive technologies (NBIC) will enable significant improvements in how, where, and what is taught in grades K-12 and will also support the lifelong learning required by a rapidly developing technological economy. Through national and state standards, half the schools in the United States will be teaching science based on the unifying principles of science and technology (NRC 1995) rather than the isolated subjects taught since before the industrial revolution. New tools for learning such as neuroscience sensors, increased quality of Internet service via guaranteed bandwidth, and a new understanding of biological feedback for self-improvement will provide new, highly efficient learning methods for all, in particular guaranteeing that all children can read by age five. Students will no longer be dependent on rigid regimentation of the classroom or schoolhouse and class schedules, as they will have courses and supplemental information available to them from numerous venues around the clock. Consider the following scenario.

The year is 2015. You enter a public school. From the outside, it appears to be much the same physical structure as schools were for 50 years. But inside is a totally different world. Teachers are busily meeting with one another and engaged in e-learning to stay current on the latest developments in education and their disciplines. They are contributing their experiences to a databank that parses the data into

information and places it on an information website for other teachers and researchers to use. Science teachers are working in a cross-disciplinary program that has been particularly fruitful — NBIC — a wonderful stew of nanotechnology, biotechnology, information technology, and cognitive technologies. NBIC has allowed these teachers to productively access and continually learn new information through advances in small biological and neurological sensors and the biofeedback they produce. A number of special needs students are working in rooms, receiving cues from a wireless network that are appropriate for their individual cognitive and physical needs as developed through NBIC. Advances in NBIC research allow for better meeting the requirements of more and more special needs students each year with fewer human resources. Each student in the community can interact with other students worldwide to share information, language, and culture. While the student population of more than 50 million students has been joined by millions of parents as lifelong learning requirements are realized, no new buildings have been required, as many students take advantage of 24/7 availability of coursework at their homes, in work areas, and at the school. The capital investment savings have been redirected into increased pay to attract and retain the highest quality teachers and curriculum developers. The line between education and recreation has blurred as all citizens visit the school building throughout the day to better their lives.

The Critical Roles of Converging Technologies

Converging technologies hold true promise to revolutionize the teaching in grades K-12 and beyond. The interplay of these technologies, each with the other, provides the opportunity for extraordinary advances in K-12 education on three fronts: content, process, and tools

Content

The recent extraordinary and rapid results of the Human Genome Project (HGP) provide for a revolution in the content of biology curriculum for K-12. The rapid completion of this project was due in a large part to the availability of IT-supported and -inspired experimental, analytical, and observational capability. While known as a “biology” project, the revolutionary advances are truly due to cross-disciplinary fertilization. CT offers K-12 education a focus that builds on the HGP accomplishments and provides content that folds in nanotechnology to understand the interactions of and to physically manipulate particles and entities at the fundamental sizes of the building blocks of life. New course content must be created that is sensitive to these developments and can be updated on an annual basis to be relevant to students’ needs and the rapidly growing state of knowledge in the research fields. New courses that delve into the aspects of intelligent, sentient life and cognitive processes must also be developed. These courses must be created in the context of state-of-the-art and state-of-the-practice biotechnology, information technology, and nanotechnology. The state of Texas has already altered its formerly strictly discipline-structured curriculum with the insertion of an Integrated Physics and Chemistry Course. The content advances called for in this essay are in the same vein as the Texas advance but a quantum jump into the future – a jump necessary to serve students of the United States in a globally competitive economy (NAP 1995).

Process

A fundamental understanding of the physical or biological basis for cognition developed in CT will allow for a revolution in the individualization of the K-12 educational process. Psychologists currently study people's responses to stimuli and their ability to control their responses given certain physical data from their bodies (popularly known as biofeedback). However, to map the various learning modalities of children, physical and biological characteristics must be associated with a child's cognitive behaviors in such a way that genotypic or phenotypic mitigations can be identified and applied. The analysis of such data will require nano-, cogno-, bio-, and information technologies that are years beyond today's capabilities, as will the presentation of educational media once the appropriate intervention or course of treatment is identified.

Technologies for measuring brain activity and assessing cognitive function, representing advances in usability and sensitivity over the current electro-, magneto-, and hemo-encephalographic technologies, will be developed that have the ability to go beyond diagnosing disorders to assessing students' learning strengths and weaknesses. This enhanced sensitivity will be enabled by advanced biotechnologies that are tuned to monitor cognitive function and will support the selection of appropriate remediation. Neurologically-based technologies will be available to assist in the remediation of learning impairments as well as to enhance the cognitive abilities of children. These technologies will extend a student's ability to concentrate and focus, to remember and retain, and to deal with stress.

Attention and memory enhancement technologies will be built upon computer-based cognitive rehabilitation technologies that are already available, as indicated in an NIH Consensus Statement (1998): "Cognitive exercises, including computer-assisted strategies, have been used to improve specific neuropsychological processes, predominantly attention, memory, and executive skills. Both randomized controlled studies and case reports have documented the success of these interventions using intermediate outcome measures. Certain studies using global outcome measures also support the use of computer-assisted exercises in cognitive rehabilitation."

Other education-related technologies include improvement of a student's attention and stress management abilities using brainwave and autonomic nervous system (ANS) biofeedback technologies. The Association for Applied Psychophysiology and Biofeedback (AAPB) has initiated a program "to assist educational and health professionals to teach children and youth to regulate their own bodies, emotions, relationships, and lives" (AAPB 2001).

Foreshadowing and early beginnings of this trend can already be seen, and it will gather momentum rapidly in the next few years. Computer software that simultaneously trains cognitive abilities directly relevant to academic performance and delivers brainwave biofeedback is used in school settings and is commercially available (Freer 2001). Biofeedback enrichment of popular video games (Palsson et al. 2001) has already been demonstrated to work as well as traditional clinical neurofeedback for attention deficit disorder. This same technology is also designed to deliver autonomic self-regulation training for stress management. Instrument functionality feedback, developed at NASA Langley Research Center, is a novel training concept for reducing pilot error during demanding or unexpected events in

the cockpit by teaching pilots self-regulation of excessive autonomic nervous system reactivity during simulated flight tasks (Palsson and Pope 1999). This training method can also teach stressed youngsters to practice autonomic physiological self-regulation while playing video games without the need for conscious attention to such practice.

Embedding physiological feedback training into people's primary daily activities, whether work or play, is a largely untapped and rich opportunity to foster health and growth. It may soon be regarded to be as natural and expected as is the addition of vitamins to popular breakfast cereals. Toymakers of the future might get unfavorable reviews if they offer computer games that only provide "empty entertainment."

Twenty years from now, physiological feedback will be embedded in most common work tasks of adults and will be integral to the school learning and play of children. Interactions with computers or computer-controlled objects will be the predominant daily activity of both adults and children, and physiological feedback will be embedded in these activities to optimize functioning and to maintain well-being and health.

Tools

CT brings distance learning of today to a true 24/7 educational resource. Telepresence and intelligent agents will allow students to investigate fundamental biological questions through online laboratories and high-fidelity simulations. The simulations will be extensions of today's state-of-the-art distance surgery and robotic surgery. Actual data and its expected variations in physical attributes such as color, density, location, and tactile tension will be available in real time. Students in cities, suburbs, and remote rural areas will all have access to the same state-of-the-art content and delivery. These tools will first be available at central locations such as schools or libraries. As hardware cost and guaranteed available bandwidth allows, each home will become a school unto itself — providing lifelong learning for children and adult family members.

Delivery of learning experiences will be designed to enhance student attention and mental engagement. This goal will be supported in the classroom and at home by digital game-based learning (DGBL) experiences that provide (1) meaningful game context, (2) effective interactive learning processes including feedback from failure, and (3) the seamless integration of context and learning (Prensky 2001). Entertaining interactive lessons are available (Lightspan Adventures™) that run on a PC or a PlayStation® game console so that they can be used both in school and after school and in students' homes.

Patented technologies are also available that "use the latest brain research to develop a wide range of early learning, language, and reading skills: from letter identification and rhyming to vocabulary and story analysis" for "children who struggle with basic language skills or attention problems" (Scientific Learning 2001).

Another set of educational tools enabled by CT, physiological monitoring, will be used to guide complex cognitive tasks. The recent proposal for NASA's Intelligent Synthesis Environment (ISE) project included an animation of a computer-aided design system responding to a user's satisfaction about a design iteration, measured via remote sensing of brainwaves. Similarly, a student's engagement in and grasp of

educational material will be monitored by brain activity measurement technology, and the presentation can be adjusted to provide challenge without frustration.

Virtual reality technologies, another tool set, will provide the opportunity for immersive, experiential learning in subjects such as history and geography. Coupled with interactive simulations, VR environments will expand the opportunities for experiences such as tending of ecosystems and exploring careers. A NASA invention called "VISCEREAL" uses skin-surface pulse and temperature measurements to create a computer-generated VR image of what is actually happening to blood vessels under the skin (Severance and Pope 1999). Just as pilots use artificial vision to "see" into bad weather, students can use virtual reality to see beneath their skin. Health education experiences will incorporate realtime physiological monitoring integrated with VR to enable students to observe the functioning of their own bodies.

Transforming Strategy

The major technical barrier for instituting CT into the K-12 curriculum is the political complexity of the curriculum development process. Curriculum is the result of the influence of a number communities, both internal and external to the school district, as shown in Figure F.3.

The CT Initiative must identify and work with all the appropriate K-12 communities to successfully create and integrate new curriculum — perhaps addressing a K-16 continuum. While teacher institutes occasionally can be useful, participatory partnering in real curriculum development promises to leave a lasting mark on more students and faculty. It is key to successful curriculum development to put together a coalition of teachers, administrators, students, parents, local citizens, universities, and industry for curriculum development. The virtual lack of any interdepartmental or cross-discipline courses in K-12 curricula is indicative of

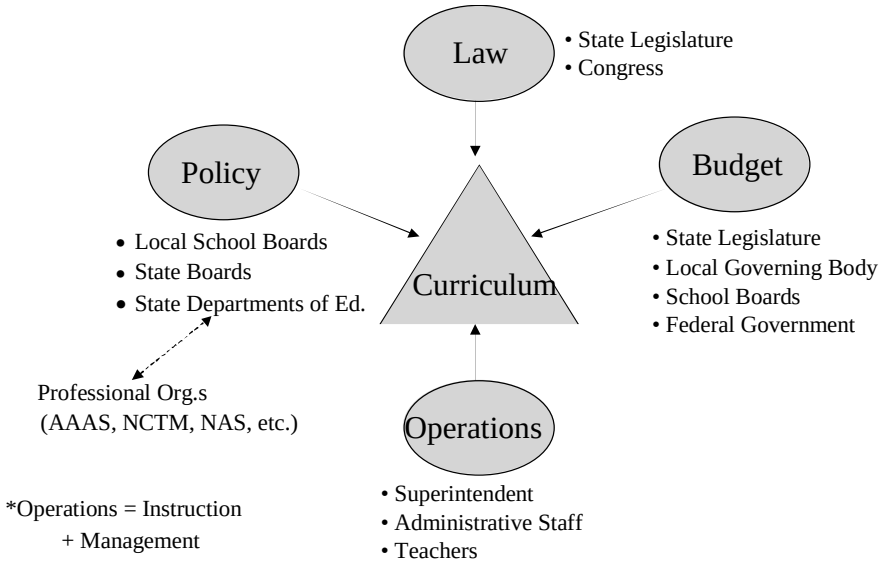

Figure F.3. The curriculum communities.

the gap that must be bridged to teach CT.

From the CT Initiative, courses can be created, but for *curriculum development*, the courses must be institutionalized or put into the context of the other courses in the school district. This institutionalization requires the involvement and support of the entire range of communities shown in Figure F.3.

There are approximately 50 million K-12 students in 15,000 school districts in the United States, its territories, and the District of Columbia. Reaching these districts or students individually would be virtually impossible. Rather, a major strategy should be to take advantage of the leverage available through impacting the national science education standards and emerging state standards (Figure F.4). At the national level, development and inclusion of CT curriculum involves development of national CT standards as a part of the national science education standards developed by the National Resource Council (NRC 1995). CT scientists should work for a regular review of the current standards and be prepared to provide CT standards as members of the review and standards committees.

Because there is no national U.S. curriculum, having national CT standards serves only an advisory function. For these standards to be used in curriculum development, they need to be accepted by state boards of education in development of their separate state standards (Figure F.3 and Figure F.4). Each state must then have courses available that meet the standards it adopts. Many states have developed statewide assessments or tests for various subjects. A major step toward implementation of CT curricula would be positioning CT questions on statewide science assessment tests.

Complementary to the development of a K-12 curriculum *per se* is the development of a CT mentality in the general population and in the next generation of teachers and parents. Thus, development of CT courses at colleges in general, and in their teacher preparation departments in particular, is desirable.

Thus the transforming strategy for educational content has the following components:

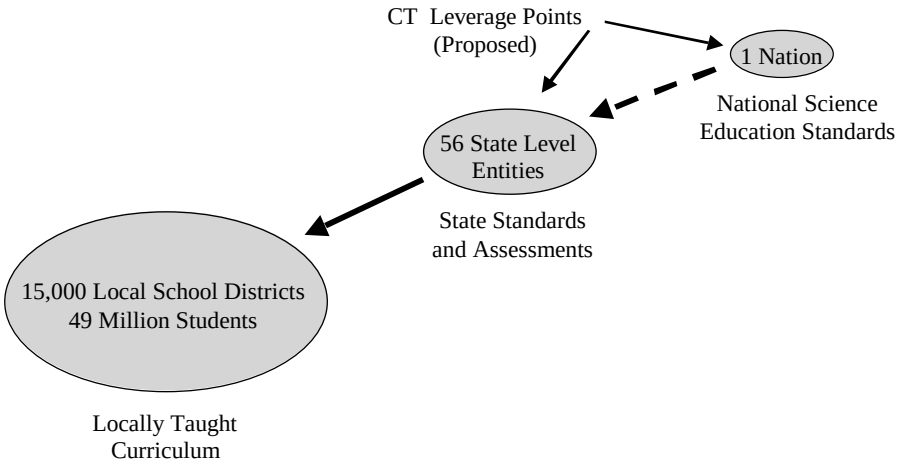

Figure F.4. Relationships between national and state standards and local school districts.

- Influence over the National Science Education Standards (NRC)
- Development of CT science content standards
- Development of CT courses for K-12 to support the CT standards
- Influence on each state's science standards and assessment instruments
- Development of CT courses for schools of education and in the general education of the next generation of university students
- Development, in cooperation with a writer of children's books, of "early reader" (ages 1-5) books containing CT concepts

Ethics

Ethical issues regarding the ability to analyze each child's capacity to learn and develop will arise. Categorization of humans relating to their abilities, and perhaps to their inferred potential in any area, may challenge many of our Western traditions and ethical values.

Implications

The implications of CT content, process, and tools for education of all children are dramatic. A specific focus would be the population of students today classified as "special education" students under IDEA (the Individuals with Disabilities Education Act – PL94-142). This includes approximately 10 percent of the entire age 3-17 cohort in the United States, or almost five and a half million children in the 6-21 year age bracket. More than one million of these children are diagnosed with speech or language impairment; 2.8 million with specific learning disabilities such as dyslexia; 600,000 with mental retardation; 50,000 with autism; and 450,000 with emotional disturbance.

In K-12 education, school district visions commonly aspire to educate all children to their full potential. The reality has been that many children are not educated to a level that allows them to be productive members of adult society, let alone to reach their own full potential. While there is some differentiation of instruction and curriculum strands (such as special education, governor's schools, alternative education, and reading and hearing resource education), the ability to diagnose individual student needs is based on failure of a child to succeed in a "standard" early curriculum. It is only after such a failure that analysis begins with the possibility of a placement into one of several available alternative strands. These strands again treat a bulk condition identified empirically from phenotypic behaviors rather than treating an individual condition analyzed from the child's genotype. Individualization or fine-tuning of treatment is accomplished through labor-intensive one-on-one teaching. Our new vision, supported by convergent technologies, anticipates a future in which today's failures to successfully educate all children are mitigated through a fundamental physical understanding and modeling of cognitive and biological capabilities and processes in the young child. Appropriate mitigation and direction are based on early anticipation of the child's individual needs rather than bulk treatment after early failures.

The Glenn Commission (National Commission on Mathematics and Science Teaching for the 21st Century, Glenn 2000) estimated that the cost of meeting its three goals of improving science teaching quality with the current teachers, developing more science and math teachers, and improving the science and math

teaching environment would cost approximately $5 billion in the first year. Roughly, this money would be used to provide teacher summer institutes, leadership training, incentives, scholarships, assessments, and coordination. Since this is aimed at all science and math teachers over a five-year program (there are 1.5 million science and math teachers for grades K-12 in the United States), CT could take early advantage of any implementation of a plan such as that proposed by the Glenn Commission.

Revisions in curriculum standards seem to take about five to ten years to develop, absent a major sea change in what is being taught. CT is a major change, and it further moves curriculum to stay current with scientific and technological advances. This will require regularly occurring curriculum reviews at the state level and the ability to adjust content and assessment with a factor of ten more efficiency than is done today. As a guide to the states, a national curriculum must also be reviewed and updated in a similarly regular way.

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EXPANDING THE TRADING ZONES FOR CONVERGENT TECHNOLOGIES

Michael E. Gorman, University of Virginia

Stimulating convergence among nano, bio, info, and cognitive science obviously will require that different disciplines, organizations, and even cultures work together. To make certain this convergence is actually beneficial to society, still other stakeholders will have to be involved, including ethicists, social scientists, and groups affected by potential technologies. To promote this kind of interaction, we first need a vision — supplied, in this case, by a metaphor.

Vision: Developing "Trading Zones," a Metaphor for Working Together

A useful metaphor from the literature on science and technology studies is the trading zone. Peter Galison used it to describe how different communities in physics and engineering worked together to build complex particle detectors (Galison 1997). They had to develop a creole, or reduced common language, that allowed them to reach consensus on design changes:

> Two groups can agree on rules of exchange even if they ascribe utterly different significance to the objects being exchanged; they may even disagree on the meaning of the exchange process itself. Nonetheless, the trading partners can hammer out a *local* coordination, despite vast *global* differences. In an even more sophisticated way, cultures in interaction frequently establish contact languages, systems of discourse that can vary from the most function-specific jargons, through semispecific pidgins, to full-fledged creoles rich enough to support activities as complex as poetry and metalinguistic reflection (Galison 1997, 783).

My colleague Matt Mehalik and I have classified trading zones into three broad categories, on a continuum:

1. *A hierarchical trading zone governed by top-down mandates.* An extreme example is Stalinist agricultural and manufacturing schemes used in the Soviet Union (Graham 1993; Scott 1998) where the government told farmers and engineers exactly what to do. These schemes were both unethical and inefficient, stifling any kind of creativity. There are, of course, top-down mandates where the consequences for disobedience are less severe, but I would argue that as we look to the future of NBIC, we do not want research direction set by any agency or group, nor do we want a hierarchy of disciplines in which one dominates the others.

2. *An equitable trading zone state in which no one group is dominant*, and each has its own distinct perspective on a common problem. This kind of trading zone was represented by the NBIC conference where different people with expertise and backgrounds exchanged ideas and participated jointly in drafting plans for the future.
3. *A shared mental model trading zone based on mutual understanding of what must be accomplished*. Horizontal or lattice styles of business management are designed to promote this kind of state. An example is the group that created the Arpanet (Hughes 1998).

Another example is the multidisciplinary global group that invented a new kind of environmentally intelligent textile. Susan Lyons, a fashion designer in New York, wanted to make an environmental statement with a new line of furniture fabric. Albin Kaelin's textile mill in Switzerland was in an "innovate or die" situation. They started a trading zone around this environmental idea and invited the architect William McDonough, who supplied a mental model based on an analogy to nature, "waste equals food," meaning that the fabric had to fit smoothly back into the natural cycle in the same way as organic waste products. The architect brought in Michael Braungart, a chemical engineer who created and monitored detailed design protocols for producing the fabric. The actual manufacturing process involved bringing still others into the trading zone (Mehalik 2000).

Note that the shared mental model did not mean that the architect understood chemical engineering, or vice-versa. All members arrived at a common, high-level understanding of waste equals food and translated that into their own disciplinary practices, while staying in constant touch with each other. The creoles that arise among Galison's communities are typically devoted to local coordination of practices. In this fabric case, we see a Creole-like phrase, "waste equals food," evolve into a shared understanding that kept different expertises converging on a new technology.

Role of Converging Technologies

Converging technologies designed to benefit society will involve trading zones with a shared mental model at the point of convergence. "Waste equals food" created a clear image of an environmental goal for the fabric network. Similar shared mental models will have to evolve among the NBIC areas.

The process of technological convergence will not only benefit from trading zones, it can play a major role in facilitating them. Consider how much easier it is to maintain a transglobal trading zone with the Internet, cell phones, and air transport. Imagine a future in which convergent technologies make it possible for people to co-locate in virtual space for knowledge exchange, with the full range of nonverbal cues and sensations available. Prototypes of new technological systems could be created rapidly in this virtual space and tested by representatives of stakeholders, who could actually make changes on the fly, creating new possibilities. The danger, of course, is that these virtual prototypes would simply become an advanced form of vaporware, creating an inequitable trading zone where technology is pushed on users who never have full information. But in that case, new trading zones for information would emerge, as they have now — witness the success of *Consumer*

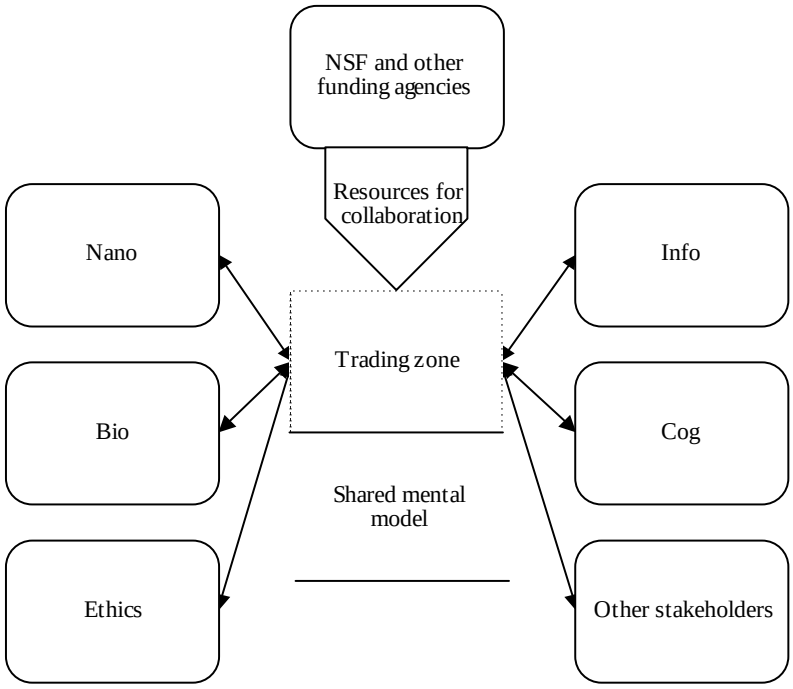

Figure F.5. Technologies converging on a trading zone seeded by resources that encourage collaboration.

Reports. It is essential that powerful new technologies for disseminating and creating knowledge be widely accessible, not limited to an elite.

Transforming Strategies

Effective trading zones around convergent technologies cannot be created simply by bringing various groups together, although that is a first step. Here, federal agencies and foundations can form a trading zone around resources (see Figure F.5) — like the role of the National Science Foundation in the National Nanotechnology Initiative. This kind of program must not micromanage the sort of research that must be done; instead, it has to provide incentives for real engagement among different cultures of expertise.

Technologies designed to improve human health, increase cognitive performance, and improve security will have to fit into global social systems. We need to create active technological and scientific trading zones built around social problems. These trading zones will require experts with depth in relevant domains. The trading zones will need to provide incentives for them to come together, including opportunities to obtain funding and to work on "sweet" technological problems (Pacey 1989). In addition, each zone will require a core group of practitioners from different disciplines to share a mental model of what ought to be accomplished.

Here, it is worth recalling that mental models are flexible and adaptable (Gorman 1992; Gorman 1998). One good heuristic for creating a flexible shared mental model

came up repeatedly during the conference: "follow the analogy of nature." Alexander Graham Bell employed this heuristic in inventing the telephone (Gorman 1997). Similarly, McDonough's "waste equals food" mental model is based on the analogy to living systems, in which all organic waste is used as food by forms of life.

Similarly, as we look at beneficial ways in which human performance can be enhanced, it makes sense to study the processes and results of millions of years of evolution, which have affected not only biological systems, but also the climate cycles of the entire planet (Allenby 2001). The pace of technological evolution is now so fast that it exceeds the human capacity to reason about the consequences. Hence, we have to anticipate the consequences — to attempt to guide new discoveries and inventions in a beneficial direction. Nature's great inventions and failures can be a powerful source of lessons and goals. As Alan Kay said, "The best way to predict the future is to create it."

We see NASA adopting this analogy to nature when it proposes aircraft that function like high-technology birds, with shifting wing-shapes. The human ear served as Alexander Graham Bell's mental model for a telephone; in the same way, a bird might serve as a mental model for this new kind of aircraft. Creating this kind of air transport system will require an active trading zone among all of the NBIC areas, built around a shared mental model of what needs to be accomplished.

Good intellectual trading zones depend on mutual respect. Hard scientists and engineers will have to learn to respect the expertise of ethicists and social scientists, and vice-versa. The ethicist, for example, cannot dictate moral behavior to the scientists and engineers. Instead, s/he has to be ready to trade expertise, learning about the science and engineering while those practitioners get a better understanding of ethical issues.

Consider, for example, a trading zone between the medical system and its users around bioinformatics. Patients will be willing to trade personal information in exchange for more reliable diagnoses. But the patients will also have to feel they are being treated with respect — like human beings, not data points — or else the trading zone will break down.

In terms of education, what this means is that we want to encourage students to go deeply into problems, not necessarily into disciplines. Elementary students do not see the world divided into academic categories; instead, they see interesting questions. As they pursue these questions, they should be encouraged to engage deeply. But the result will be new kinds of expertise, not necessarily easily labeled as "physics," "chemistry," or "biology." The best trading zones are built around exciting problems by practitioners eager to create the knowledge necessary for solutions. And every such trading zone ought to include practitioners concerned about the social dimensions of technology.

Communication is the key to a successful trading zone. Students need to be given opportunities to work together in multidisciplinary teams, sharing, arguing, and solving difficult, open-ended problems together. Teachers need to scaffold communication in such teams, helping students learn how to present, write, and argue constructively. We have a long tradition of doing this in our Division of Technology, Culture, and Communication in the Engineering School at the University of Virginia (http://www.tcc.virginia.edu).

Estimated Implications

The great thing about trading zones is that successful ones expand, creating more opportunities for all of us to learn from each other. Hopefully, the first NBIC meeting has provided a foundation for such a trading zone between nano, bio, info, and cogno practitioners — and those in other communities like ethics, politics, and social relations.

We must remember to accompany the creation of convergent trading zones with detailed studies of their development. One of the most valuable outcomes would be a better understanding of how to encourage the formation of convergent, multidisciplinary trading zones.

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BIOLOGICAL LANGUAGE MODELING: CONVERGENCE OF COMPUTATIONAL LINGUISTICS AND BIOLOGICAL CHEMISTRY

Judith Klein-Seetharaman and Raj Reddy, Carnegie Mellon University

How can we improve the nation's productivity and quality of life in the next 10 to 20 years? The nation's performance is dependent on functions of the human body, since they directly or indirectly determine human ability to perform various tasks. There are two types of human ability: (1) "inherent abilities," tasks that humans are able to perform, and (2) "external abilities," tasks that we cannot perform *per se*, but for which we can design machines to perform them. Both categories have individually experienced groundbreaking advances during the last decade. Our inherent abilities in terms of fighting diseases, repair of malfunctioning organs through artificial implants, and increased longevity have greatly improved, thanks to advances in the medical and life sciences. Similarly, technology has provided us with remarkable tools such as smaller and more efficient computers; the Internet; and safer, cleaner, and cheaper means of transport.

Integration of Inherent and External Human Abilities

Advancing our society further necessitates a better integration between the inherent and external abilities. For example, interfacing computers with humans need not require keyboard and mouse: ongoing efforts advance utilization of speech interfaces. But ultimately, it would be desirable to directly interface with the human brain and other organs. This will require further advances in elucidating the fundamental biological mechanisms through which humans think, memorize, sense, communicate, and act. Understanding these mechanisms will allow us to (a) modify our inherent abilities where natural evolution does not feel any pressure for improvement and (b) design interfaces that connect our inherent abilities with external abilities.

Grand Challenge: Mapping Genome Sequence Instructions to Inherent Abilities

How can we aim to understand complex biological systems at a level of detail sufficient to improve upon them and build interfaces to external machines? In principle, all the information to build complex biological systems is stored in an "instruction manual," an organism's (e.g., a human's) genome. While we have recently witnessed the elucidation of the entire human genome sequence, the next logical grand challenge for the coming decade is to map the genome sequence information to biological functions. Interfacing between biological functions and artificially manufactured devices will require improved structure-property understanding as well as manufacturability at a multiscale level ranging from Ångstrom-sized individual components of biological molecules to macroscopic responses. This will be possible through existing and future advances in nanotechnology, biological sciences, information technology, and cognitive sciences (NBIC).

Outline

The sequence function mapping question is conceptually similar to the mapping of words to meaning in linguistics (Figure F.6). This suggests an

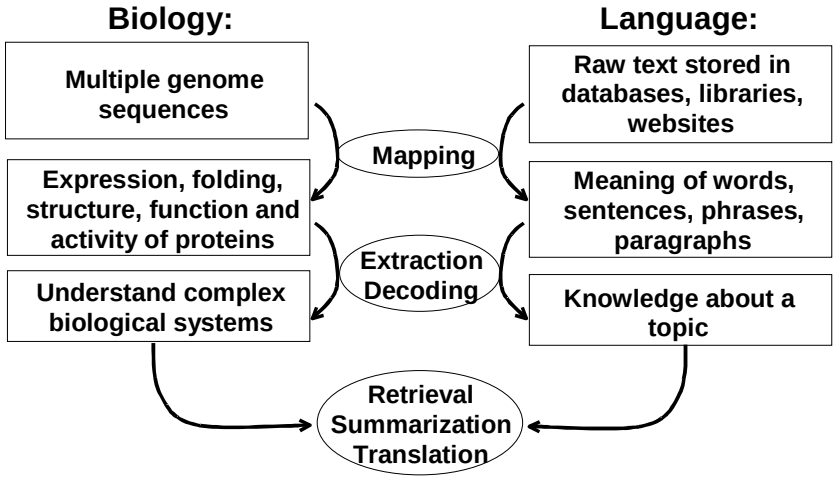

Figure F.6. Analogy between language and biology, which forms the basis for the convergence of computational linguistics and biological chemistry.

opportunity to converge two technologies to address this challenge: computational linguistics and biological chemistry, via "biological language modeling." The term "biological chemistry" is used here to stand for interdisciplinary studies of biological systems, including biochemistry, molecular biology, structural biology, biophysics, genetics, pharmacology, biomedicine, biotechnology, genomics, and proteomics. The specific convergence of linguistics and biological chemistry is described below under the heading, "The Role of Converging Technologies: Computational Linguistics and Biological Chemistry." Its relation to the more general convergence with NBIC is described in section, "The Role of Converging Technologies: NBIC and Biological Language Modeling." Two specific applications of linguistic analysis to biological sequences are given in "The Transforming Strategy," to demonstrate the transforming strategy by example. If we can solve the sequence function mapping question, the implications for human performance and productivity are essentially unlimited. We have chosen a few practical examples to illustrate the scope of possibilities ("The Estimated Implications"). Implications for society are sketched in "Implications for Society," followed by a brief summary.

The Role of Converging Technologies: Computational Linguistics and Biological Chemistry

Complex biological systems are built from cells that have differentiated to perform specialized functions. This differentiation is achieved through a complicated network of interacting biological molecules. The main action is carried out by proteins, which are essentially nano-sized biological machines that are composed of strings of characteristic sequences of the 20 amino acid building blocks. The sequences of the strings are encoded in their entirety in the genome. The linear strings of amino acids contain in principle all the information needed to fold a protein into a 3-D shape capable of exerting its designated function. With the advent of whole-genome sequencing projects, we now have complete lists of all the protein sequences that define the complex function carried out by the sequenced organisms — hundreds to thousands in bacteria and tens of thousands in humans. Individual proteins and functions have been studied for decades at various levels — atomic to macroscopic. Most recently, a new field has evolved, that of proteomics, which looks at all the proteins in a cell simultaneously. This multitude of data provides a tremendous new opportunity: the applicability of statistical methods to yield practical answers in terms of likelihood for biological phenomena to occur.

The availability of enormous amounts of data has also transformed linguistics. In language, instead of genome sequences, raw text stored in databases, websites, and libraries maps to the meaning of words, phrases, sentences, and paragraphs as compared to protein structure and function Figure F.6). After decoding, we can extract knowledge about a topic from the raw text. In language, extraordinary success in this process has been demonstrated by the ability to retrieve, summarize, and translate text. Examples include powerful speech recognition systems, fast web document search engines, and computer-generated sentences that are preferred by human evaluators in their grammatical accuracy and elegance over sentences that humans build naturally. The transformation of linguistics through data availability has allowed convergence of linguistics with computer science and information technology. Thus, even though a deep fundamental understanding of language is still

missing, e.g., a gene for speech has only been discovered a few months ago (Lai et al. 2002), data availability has allowed us to obtain practical answers that fundamentally affect our lives. In direct analogy, transformation of biological chemistry by data availability opens the door to convergence with computer science and information technology. Furthermore, the deeper analogy between biology and language suggests that successful sequence function mapping is fundamentally similar to the ability to retrieve, summarize, and translate in computational linguistics. Examples for biological equivalents of these abilities are described below under "The Estimated Implications."

The Role of Converging Technologies: NBIC and Biological Language Modeling

The strength of the analogy between biology and language lies in its ability to bridge across scales — atomic, nanostructural, microstructural, and macroscopic — enabling profit from the convergence of other disciplines (Figure F.7). Ideally, we would like to correlate complex biological systems, including their most complex abilities — the cognitive abilities of the brain, such as memory — with the individual atoms that create them. Rapid advances currently occur at all scales because of the convergence of technologies, allowing us to collect more data on natural systems than we were ever able to collect before. The data can be analyzed using information technology at all levels of the hierarchy in scale. Furthermore, mapping can involve any levels of the hierarchy, e.g., atomic macroscopic or nanostructural microstructural. The language analogy is useful here because of the hierarchical organization of language itself, as manifested by words, phrases, sentences, and paragraphs.

The Transforming Strategy

One test for convergence of technologies is that their methods are

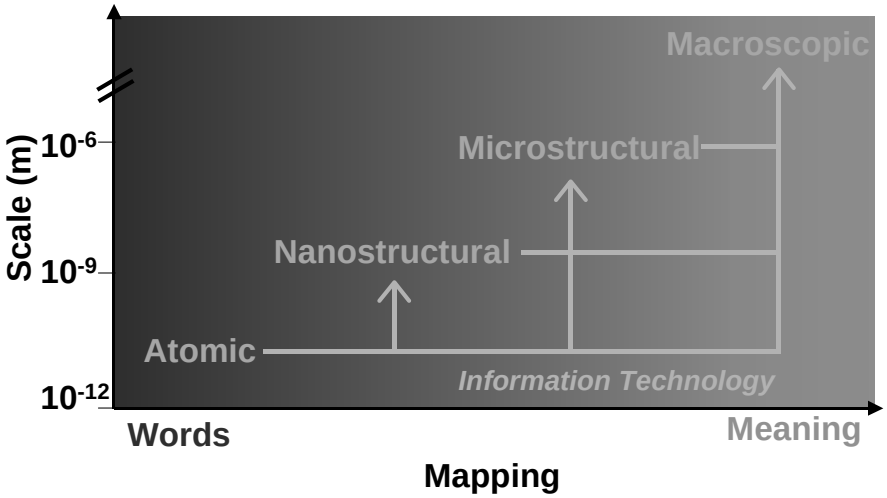

Figure F.7. Biological language modeling allows bridging across scales via the mapping of words to meaning using information technology methods, in particular computational linguistics.

interchangeable, i.e., language technologies should be directly applicable to biological sequences. To date, many computational methods that are used extensively in language modeling have proven successful as applied to biological sequences, including hidden Markov modeling, neural network, and other machine learning algorithms, demonstrating the utility of the methodology. The next step is to fully explore linguistically inspired analysis of biological sequences. Thus, the Carnegie Mellon and Cambridge Statistical Language Modeling (SLM) Toolkit, utilized for natural language modeling and speech recognition in more than 40 laboratories worldwide, was applied to protein sequences, in which the 20 amino acids were treated as words and each protein sequence in an organism as a sentence of a book. Two exemplary results are described here.

1. In human languages, frequent words usually do not reveal the content of a text (e.g., "I", "and", "the"). However, abnormalities in usage of frequent words in a particular text as compared to others can be a signature of that text. For example, in Mark Twain's *Tom Sawyer*, the word "Tom" is amongst the top 10 most frequently used words. When the SLM toolkit was applied to protein sequences of 44 different organisms (bacterial, archaeal, human), specific n-grams were found to be very frequent in one organism, while the same n-gram was rare or absent in all the other organisms. This suggests that there are organism-specific phrases that can serve as "genome signatures."
2. In human languages, rare events reveal the content of a text. Analysis of the distribution of rare and frequent n-grams over a particular protein sequence, that of lysozyme, a model system for protein folding studies, showed that the location of rare n-grams correlates with nucleation sites for protein folding that have been identified experimentally (Klein-Seetharaman 2002). This striking observation suggests that rare events in biological sequences have similar status for the folding of proteins, as have rare words for the topic of a text.

These two examples describing the usage of rare and frequent "words" and "phrases" in biology and in language clearly demonstrates that convergence of computational linguistics and biological chemistry yields important information about the mapping between sequence and biological function. This was observed even when the simplest of computational methods was used, statistical n-gram analysis. In the following, examples for the potential benefits of such information for improving human health and performance will be described.

The Estimated Implications

Implications for Fundamental Understanding of Properties of Proteins

The convergence of linguistics and biology provides a framework to connect biological information gathered in massive numbers of studies, including both large-scale genome-wide experiments and more traditional small-scale experiments. The ultimate goal is to catalogue all the words and their respective meanings occurring in genomic sequences in a "biological dictionary." Sophisticated statistical language models will be able to calculate the probabilities for a specific amino acid within a protein context. It will be possible to examine what combinations of amino acid sequences give a meaningful sentence, and we will be able to predict where spelling mistakes are inconsequential for function and where they will cause dysfunction.

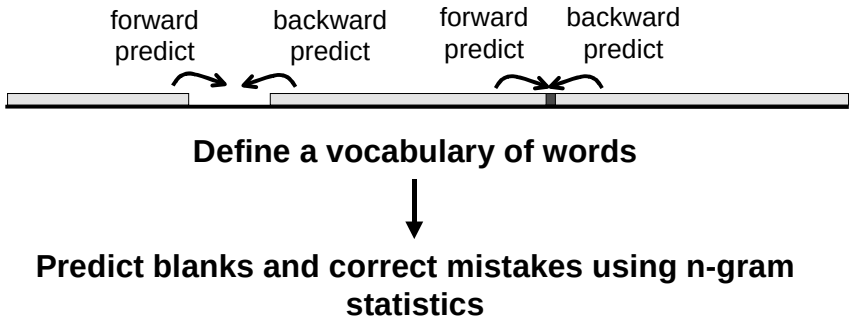

Figure F.8. Opportunity for biological language modeling in genome sequences.

Cataloguing Biological Languages at Hierarchical Levels: Individual Proteins, Cell Types, Organs, and Related and Divergent Species

The language modeling approach is applicable to distinguishing biological systems at various levels, just as language varies among individuals, groups of individuals, and nations. At the most fundamental level, we aim at deciphering the rules for a general biological language, i.e., discovering what aspects are common to all sequences. This will enhance our fundamental understanding of biological molecules, in particular how proteins fold and function. At the second level, we ask how differences in concentrations, interactions, and activities of proteins result in formation and function of different cell-types and ultimately of organs within the same individual. This will allow us to understand the principles underlying cell differentiation. The third level will be to analyze the variations among individuals of the same species, the single nucleotide polymorphisms. We can then understand how differences in characteristics, such as intelligence or predisposition for diseases, are encoded in the genome sequence. Finally, the most general level will be to analyze differences in the biological languages of different organisms, with varying degree of relatedness.

Ideally, all life on earth will be catalogued. The impact on understanding complexity and evolution of species would be profound. Currently, it is estimated that there are 2-100 million species on earth. While it is not feasible to sequence the genomes of all the species, language modeling may significantly speed up obtaining "practical" sequences (Figure F.8). One of the bottlenecks in genome sequencing is the step from draft to finished sequence because of error correction and filling of gaps. However, if we define a vocabulary of the words for an organism from a partial or draft sequence, we should be able to predict blanks and correct mistakes in forward and backward directions using language modeling.

Retrieval, Summarization, and Translation of Biological Sequences

As in human language modeling, success in biological language modeling will be measured by the capacity for efficient (1) retrieval, (2) summarization, and (3) translation:

1. When we desire to enhance the performance of a specific human ability, we can *retrieve* all the relevant biological information required from the vast and complex data available.

Figure F.9. Opportunity for biological language modeling to overcome biotechnological challenges. Misfolding of human proteins in bacterial expression systems is often a bottleneck.

2. We can *summarize* which proteins of a pathway are important for the particular task, or which particular part of a key protein is important for its folding to functional 3-D structure. This will allow modifications of the sequences with the purpose of enhancing the original or adding a new function to it. Successful existing examples for this strategy include tagging proteins for purification or identification purposes.
3. Finally, we can *translate* protein sequences from the "language" of one organism into that of another organism. This has very important implications, both for basic sciences and for the biotechnology industry. Both extensively utilize other organisms, i.e., the bacterium *E. coli*, to produce human proteins. However, often proteins cannot be successfully produced in *E. coli* (especially the most interesting ones): they misfold, because the environment in bacterial cells is different from that in human cells (Figure F.9). Statistical analysis of the genomes of human and *E. coli* can demonstrate the differences in rules to be observed if productive folding is to occur. Thus, it should be possible to alter a human protein sequence in such a way that it can fold to its correct functional 3-D shape in *E. coli*. The validity of this hypothesis has been shown for some examples where single point mutations have allowed expression and purification of proteins from *E. coli*. In addition to the traditional use of *E. coli* (or other organisms) as protein production factories, this translation approach could also be used to add functionality to particular organisms.

Implications for Communication Interfaces

The ability to translate highlights one of the most fundamental aspects of language: a means for communication. Knowing the rules for the languages of different organisms at the cellular and molecular levels would also allow us to communicate at this level. This will fundamentally alter (1) human-human, (2) human-other organism, and (3) human-machine interfaces.

1. Human-human communication can be enhanced because the molecular biological language level is much more fundamental than speech, which may in the future be omitted in some cases as intermediary between humans. For example, pictures of memory events could be transmitted directly, without verbal description, through their underlying molecular mechanisms.

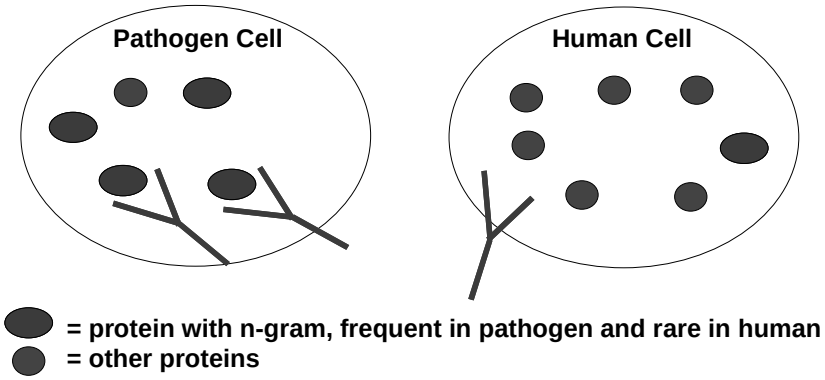

Figure F.10. Opportunity for biological language modeling to dramatically speed vaccine or drug development by simultaneously targeting multiple proteins via organism-specific phrases.

2. The differences in language between humans and other organisms can be exploited to "speak" to a pathogen in the presence of its human host (Figure F.10). That this may be possible is indicated by the observation of organism-specific phrases described in "The Transforming Strategy." This has important implications for the fight against bioterrorism and against pathogens in general to preserve and restore human health. The genome signatures should dramatically accelerate vaccine development by targeting pathogen-specific phrases. The advantage over traditional methods is that multiple proteins, unrelated in function, can be targeted simultaneously.
3. Finally, there are entirely novel opportunities to communicate between inherent and external abilities, i.e., human (or other living organisms) and machines. Using nanoscale principles, new materials and interfaces can be designed that are modeled after biological machines or that can interact with biological machines. Of particular importance are molecular receptors and signal transduction systems.

Implications to Rationalize Empirical Approaches

The greatest exploitation of the sequence structure/function mapping by computational linguistics approaches will be to rationalize empirical observations. Here are two examples.

1. The first example concerns the effect of misfolding of proteins on human health. The correlation between the distribution of rare amino acid sequences in proteins and the location of nucleation sites for protein folding described above is important because misfolding is the cause of many diseases, including Alzheimer's, BSE, and others, either because of changes in the protein sequence or because of alternative structures taken by the same sequences. This can lead to amorphous aggregates or highly organized amyloid fibrils, both interfering with normal cell function. There are databases of mutations that list changes in amyloid formation propensity. Studying the linguistic properties of the sequences of amyloidogenic wild-type and mutant proteins may help rationalizing the mechanisms for

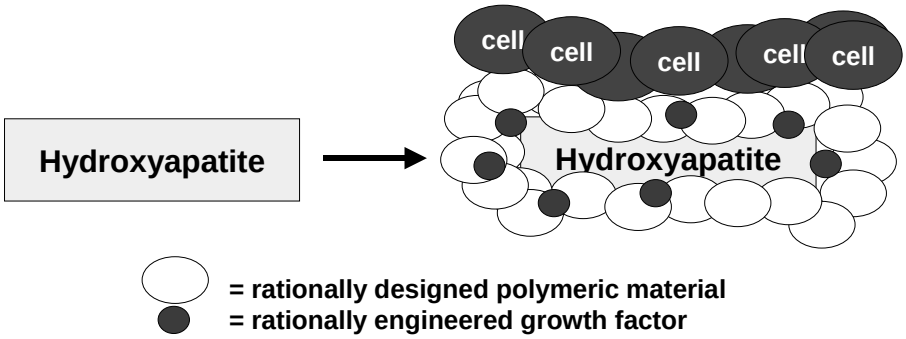

Figure F.11. Opportunity for biological language modeling to rationalize tissue engineering via engineering of growth factors and artificial materials.

misfolding diseases, the first step towards the design of strategies to treat them.

2. The second example is in tissue engineering applications (Figure F.11). The sequence structure/ function mapping also provides the opportunity to engineer functionality by rationalized directed sequence evolution. Diseased or aged body parts, or organs whose performance we might like to enhance, all need integration of external materials into the human body. One typical application is bone tissue engineering. The current method to improve growth of cells around artificial materials such as hydroxyapatite is by trial and error to change the function of co-polymers and of added growth factors. Mapping sequence to function will allow us to rationally design growth factor sequences that code for altered function in regulating tissue growth.

Implications for Society

The above scenario has important implications for economic benefits, including cheaper and faster drug development, overcoming bottlenecks in biotechnology applications, cheaper and better materials and machines that perform old and new tasks, and environmental benefits. A key challenge will be to maintain reversibility in all changes that are made to living organisms to prevent unwanted environmental catastrophes, such as predominance of new organisms with enhanced capabilities in the environment. These new technologies require drastic changes in education. Human learning, memory, and creativity — which are likely to increase as a result of the revolutions in biology — have to be steered towards attaining literacy in health and biology for all citizens. Close collaboration between academic and industrial partners will allow universities to focus on fundamental advances, keeping in mind the implications and potential applications that will be evaluated and realized by industry.

Summary

Human performance and the nation's productivity will increase drastically if existing and new biological knowledge is exploited by statistical methods to obtain practical answers to the fundamental questions:

- How can we enhance human inherent abilities?
- How can inherent and external abilities be better integrated?

The analogy between language and biology will provide a framework for addressing these questions through convergence of computational linguistics with biological chemistry within the broader context of NBIC. The challenge is to achieve successful mapping of genome sequence to structure and function of biological molecules. It would then be possible to integrate man-made machines into the human body with interfaces at the cellular and molecular level, for example, sensors for biological, chemical, or physical changes in the environment. Artificial organs will perform traditional functions better than youthful, healthy natural organs, or be able to perform new functions. By exploiting differences in languages between different organisms, novel strategies to fight pathogenic infections will emerge. New functions will be built into organisms that lack them. The maximum benefit will be possible if all knowledge is catalogued in a way that it can be accessed efficiently via computers today and in the future by nanomachines of all kinds. The biology-language analogy provides the means to do so if an encyclopedia for vocabulary and rules of biological language can be developed.

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A

B

C

D

E

F

G

H

I

M

Q

R

S

T

U

V

W

X

Y

Z

APPENDIX C. INDEX OF TOPICS

A

B

C

F

G

J

K

L

M

S

W

X

Subject: Support for the National Bioeconomy Blueprint

To whom it may concern,

My name is Paul Smith and I am urging you to move forward with the National Bioeconomy Blueprint. I am 21 years old and a recent college graduate. I am incredibly gracious towards the National Institute of Health and National Science Foundation for supporting my scientific education, as I have participated in two summer research experiences and been awarded two small research grants for my scientific. As a result, I started a salaried job two weeks after my graduation. I now work as a data-scientist at a non-profit laboratory financed by billionaire John Flatley developing therapies for cystic fibrosis. Pushing the National Bioeconomy Blueprint forward will ensure that the United States remains the global leader in scientific training and research development. My future and so many other young professionals are depending on your administration's leadership in pushing this forward.

Thank you,

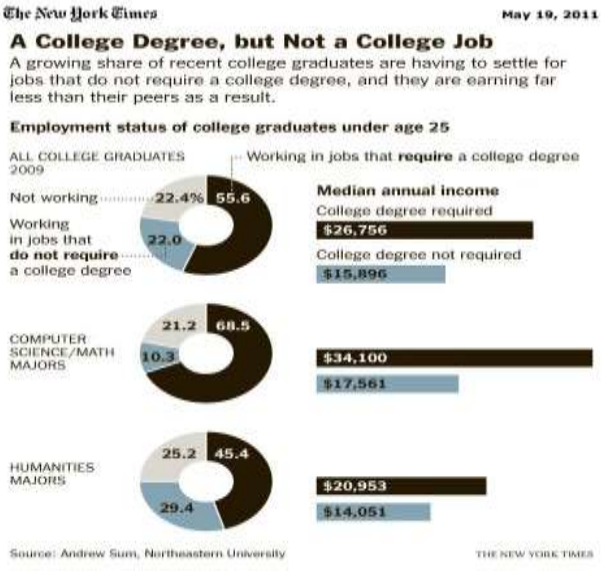
Paul T. Smith Jr.

<u>America's Innovation Corps:</u> A recommendation to the Office of Science & Technology Policy for harnessing biological research innovations to meet national challenges while creating high-wage, high-skill jobs.

The New Jersey Community College Consortium for Workforce & Economic Development (19 NJ public community colleges with 65 campus locations serving almost 400,000 NJ residents annually) in partnership with BioNJ (representing New Jersey's biotech and life science employers) and the New Jersey Business and Industry Association (the nation's largest employer member organization with over 22,000 member NJ companies) teamed with Innovation America on the development last month of **America's Innovation Corps**; "a plan to create up to 400,000 full time jobs for unemployed and under employed recent college graduates, America's next generation of knowledge workers."

We are pleased to have this opportunity to respond (October 11, 2011) to the OSTP request for "recommendations for harnessing biological research innovations to meet national challenges in health, food, energy and the environment while creating high-wage, high-skill jobs." We propose that the Office of Science & Technology Policy incorporate the **America's Innovation Corps** concept in the development of a "National Bioeconomy Blueprint" and offer to immediately institute a pilot in New Jersey. We believe that doing so will better leverage our investments in biological research and development to immediately employ unemployed and under employed recent college graduates in the biotech, life science and biohealth industry providing valuable experience and access to bioscience careers of the future and improvement in the lives of all Americans.

<u>THE PROBLEM:</u> Over 20% of recent college graduates are unemployed. Unfortunately, recent college graduates do not generally qualify for federal/state unemployment benefits. In addition, many of the recent college graduates who have secured employment are working part-time or in (50%) of the jobs that do not require a college education.



<u>The Solution</u>: A practical solution to provide meaningful employment for up to 400,000 unemployed or under employed recent college graduates by creating employment opportunities in innovative and high growth businesses including biohealth, bioscience and life sciences (a designated NJ Key Industry Sector).

<u>OVERVIEW</u>: In the U.S. today, there are over 2 million private businesses and approximately 17,000 public companies that have economic and growth challenges and are reluctant to hire in this uncertain economic time (3,100 NJ biotech & life science employers with just over 100,000 employees). There are also 13.1 million

unemployed individuals in the US that need and want to go to work (over 400,000 in NJ), including 5.1 million college graduates.

THE PROPOSED PROGRAM: A plan to place qualified college graduates in full time jobs with growing small employers utilizing existing resources. The program will be administered at the state level using New Jersey as the pilot through public community colleges, public 4-year colleges and graduate universities to recruit candidates, link to local employers and fiscally manage the program. A federal agency with existing ties to institutions of higher education and an established funding mechanism in place will be engaged and given program oversight responsibilities. An example, which has been recently launched, is the Innovation Corps (I-Corps) program of the National Science Foundation. The goal of the I-Corps program is to connect NSF-funded scientific research with the technological, entrepreneurial and business communities to help create a stronger national ecosystem. The result is innovation to couple scientific discovery with technology development and societal needs. Other federal agencies such as Labor, Commerce, NIH and Education also have established mechanisms to fund higher education institutions.

The program will provide unemployed and under employed recent college graduates a meaningful and innovative employment experience. They will have the opportunity to learn about and participate in the process of transforming and harnessing scientific and engineering discoveries into innovative applications to solving problems in bioscience. Members of the private sector—including technology developers, entrepreneurs, business leaders, venture capitalists, and others from private industry—will provide critical support of this effort as mentors in partnership with participating college faculty.

Implemention & Budget: The pilot initiative will include the 19 New Jersey community colleges and 3 public colleges and universities over 18 months. This will provide a 6 to 12 month **America's Innovation Corps** job experience for up to 1,800 recent unemployed or under employed graduates with local New Jersey bioscience employers. At the national level this would be replicated to include up to 2,000 community colleges and universities and as many as 400,000 recently unemployed or under employed college graduates.

The participating community colleges and universities will assign faculty mentors to work with each of the **America's Innovation Corps** participants and local bioscience, life science and bio-health employers. The program's focus will be on small growth employers of less than 250 employees. The participants will be full-time employees of the participating employers for a period of 6-18 months with salary subsidy and offered full-time unsubsidized employment at the program's conclusion.

Make no mistake about it, the individual participants will be full-time although temporary employees of the participating local employers during the 6 – 18 month program period. In addition to their full-time employment duties at each company, the participants under the direction of faculty and employers will also be assigned to solve a specific business or science problem identified as important to the employer's goals. The research and innovation outcome will be a part of the participants work tasks and documented in a published report to the employers, faculties and key stakeholders by *Innovation America*.

Anticipating that the vast majority of participants will become full-time employees upon completion of the 6-18 month subsidized employment period, we propose that local participating employers that hire **America's Innovation Corps** participants on a full time

basis, would be eligible to receive a wage tax credit of 50% of each individual's annual wages if that individual is retained as a full time employee for an additional 12 months following the America's Innovation Corps project job experience.

The pilot in New Jersey will cost approximately $50 million over 18 months employing up to 1,800 recent unemployed and under employed NJ college graduates. Once implemented at the national level, the cost would be approximately $3 billion. It is anticipated that each participant would be employed at an annual salary of approximately $50,000 plus benefits with a one time wage grant subsidy of up to $25,000 per participant. The federal funds would be matched by a like or greater amount in-kind from the participating employers as salary and benefits.

PROGRAM OUTCOMES:

- Nationally as many as 400,000 unemployed or under employed recent college graduates will receive meaningful full-time employment and valuable work experience plus an introduction in the application of innovation in solving real business and science problems. 1,800 in the New Jersey pilot.

- Up to 200,000 US employers will acquire qualified employees to develop innovative business solutions. 600 in New Jersey pilot.

- 1,000 community colleges and universities will cultivate better partner relationships with local employers. These newly formed partnerships will help foster the development of industry specific local curricula and enhanced employment opportunities. 20 community colleges & universities in the New Jersey pilot.

- A new tax credit program for employers (to be developed) could be implemented for the hiring of unemployed or under employed college graduates and current part time college undergraduate students

The local New Jersey partners of the New Jersey Community College Consortium for Workforce & Economic Development, BioNJ and the New Jersey Business and Industry Association will team with Innovation America to provide the project management expertise to successfully execute the initiative and evaluate the outcomes.

The biotechnology industry requires highly skilled workers to staff the research laboratories which are developing the innovations which will build the bioeconomy.

Such workers need direct training in the research laboratory which has traditionally come as a byproduct of government funding of scientific research (predominately NSF and NIH). Notably though, while NSF specifically incorporates the training of such students (the future workers of the biotech industry) into its funding decisions, NIH does not.

In the past, this has not been a major issue, however, the projected contraction/train wreck in regard to NIH funding of biomedical research is resulting in reductions in enrollment in biomedical science graduate programs nationwide. Basically, if the faculty whose research programs are training these students do not get funding, there are no resources for graduate students to perform the expensive scientific experiments necessary for their training.

Since NIH does not place any emphasis on training in funding decisions for its major grant award (the "RO1"), laboratories who take on the training of graduate students (who are often less productive than other employees who already are trained) the current funding climate puts the training of graduate students at great risk.

Unless this is dealt with soon at the level of high level policy, there will be a significant shortage in available staffing for our biotechnology research efforts between 5-10 years down the line (students entering graduate training for the Ph.D. in a life science in fall 2012 will complete training somewhere between 2017-2022 depending on whether postdoctoral studies are pursued). Without these critical workers, the future status of the industry is in doubt.

This will also result in further tax base erosion because the students who are not admitted this year who otherwise will be will not have the skills necessary to take these highly paid jobs.

One thing to note, the unemployment rate for biomedically trained Ph.D.s is still extremely low even with the current state of the economy. We are not training too many now and only shortages for industrial positions can be projected with the current trends. I am guessing that we will admit 1/2 or less students to our MS/Ph.D. degree program this year than in the past several years due to the current status of biomedical research funding.

Best,

--
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This information is provided in response to OSTP's Request for Information: Building a 21st Century Bioeconomy.

Clark A. Miller, Associate Director, Consortium for Science, Policy & Outcomes, Arizona State University

Expanding the Bioeconomy Workforce for the 21st Century

In building a workforce for a 21st century bioeconomy in the United States, it will be essential to consider not only the science and engineering workforce but also what might be termed the "allied science and engineering professions". Just as the health care industry needs more than doctors to thrive, and hence recognizes the need to train people in allied health professions, so, too, the bioeconomy will require more than just biological scientists and bioengineers. A critical part of developing the 21st century bioeconomy workforce, therefore, will be identifying the additional required elements of this broader workforce and ensuring that the national's educational institutions are prepared to meet these demands. Below are some examples of important workforce demands that are likely to emerge:

- **Policy for the 21st century bioeconomy**: as identified in request for information, policy and regulation form a critical context for the new bioeconomy and will provide either support for or barriers to the development of bio-based industries. The 21st century bioeconomy will require policy professionals at local, state, and federal levels who are prepared with the knowledge and skills necessary to develop and adapt over time robust policies supporting the bioeconomy, ranging from policies to support investment and innovation to policies ensuring the safety and efficacy of new bio-products. Yet, strikingly, very few opportunities exist at universities in the United States for students to receive training even in the general field of science and technology policy let alone in the narrower field of policy for a bioeconomy.
- **Communication for the 21st century bioeconomy**: Every country with an emerging bioeconomy has already encountered widespread public controversy, and as the bioeconomy expands, accompanying public concerns are likely to continue to grow. In the United States, public controversies involving the bioeconomy have occurred from the 1980s onward and have included opposition to the release of genetically engineered organisms, human cloning, and stem cell research, as well as widespread public concerns about drug safety and food safety. The 21st century bioeconomy will require communications professionals who have the knowledge and skills not only to understand and effectively communicate the nuanced complexities of modern bioeconomies to skeptical publics but also to engage those publics in robust dialogues about public values and the bioeconomy and communicate the results effectively to science, engineering, business, and policy leaders. Again, opportunities for this kind of training in US universities are rare that include both preparation in the kinds of communication skills necessary as well as knowledge of the emerging bioeconomy for communication purposes.

- **Innovation for the 21st century bioeconomy**: Innovation and entrepreneurship are increasingly emphasized on university campuses, providing an important foundational element for the 21st century bioeconomy. But efforts will have to be made to ensure that these initiatives reach students in the biosciences, not just business and engineering. Students in business and management fields will need appropriate training for work in the bioeconomy. Students in public policy, law, and administration will also require skills in understanding and developing appropriate policies to support the necessary innovation systems and ecosystems necessary at federal, state, and local levels to ensure that the US bioeconomy remains competitive in global contexts. Finally, it is worth noting that, consistent with recent NIH and NSF initiatives in the responsible conduct of research, scientists and engineers trained for the bioeconomy will need appropriate training in what might be termed "responsible innovation" in an arena in which fundamental human values are at stake.

One vehicle for addressing the demand for professionals with the knowledge and skills necessary to support the US bioeconomy is via professional master's degrees targeted at relevant fields. Professional science master's (PSM) degrees have been touted as a solution to the problem of a shortfall of scientists and engineers with professional training, while also expanding exposure of scientists and engineers to business and policy topics. With some modification, PSM degrees can also provide training for future bioeconomy professionals in the fields described above as well as other relevant non-technical fields. Such programs would provide both an expanded understanding of the fundamentals of the bioeconomy, including its science and engineering foundations, while focusing principally on the professional skills and knowledge required to support the bioeconomy in specific fields. Examples of the latter kind of programs include the *Professional Science Master's in Science & Technology Policy* at Arizona State University and, at Rice University, PSM degrees in *Environmental Analysis and Decision Making* and *Biosciences Research and Health Policy*. NSF, NIH, USDA, and other federal agencies should be encouraged to develop strategies for supporting and enhancing the ability of universities to prepare students for the full range of professions required to support a globally competitive bioeconomy in the US in the 21st century.

Michael I. Lerman, M.D., Ph.D.
Cancer-causing genes Expert,
National Cancer Institute,
Retired, September 2008
Email: [redacted]

October 22, 2011

This is in response to "Request for Information: Building A 21st Century Bioeconomy" published by "Office of Science and Technology Policy (OSTP)" in the Federal Register/Vol. 76, No.196/Tuuesday, October 11, 2011/Notices

Cancer was always present in human populations: there is evidence of cancer in our ancestors living in the Stone Age and Ancient Civilizations (Egyptians mummies e. g.). Nova days in The USA one of two people and one of seven children die of cancer. This is unbearable and puts on the society enormous psychological and economical constrains.

Clearly, as President Obama suggested development of "…**smart anti-cancer therapeutics that kill cancer cells and leave their normal neighbors untouched"** becomes a National Priority of the First Order. Obtaining a universal (not personalized) and relatively cheep cure for cancer will also have a global impact (and is in the interest of humanity as a whole).

These days the cancer research community is celebrating the 40 years anniversary of the "War on Cancer" a US National directive inaugurated by President Richard Nixon in 1971. The discovery of cancer causing and cancer driving genes and the Genome sequence led to efforts to find "smart targeted drugs" to cure cancer. However, despite the shameful hype in scientific literature and in popular press, leading oncologists have already accepted that cancer is not curable and the costly (~5 billions/per drug) "smart targeted drugs" we are using will convert cancer into a chronic "smoldering" illness with suffering and a shortened life since cancer cells quickly develop resistance to single or drug combinations. Obviously, the further costly hunt for cancer targeting "smart drugs" is a dead end and a waste of resources and patients lives and should be abandoned. But "big Pharma" and NCI supported researchers are still looking for new costly (~1 billion) smart targeted drugs (which have off-target-targets!) to which cancers quickly develop resistance and accelerate metastasis.

However I personally believe that the War on Cancer was indeed very successful and we have now the knowledge how to treat and cure cancer by combined gene therapy (CGTC). We know the cancer causing genes and the specific cell targets the genes in appropriate episomal expression vectors should be delivered. Our knowledge of such vectors (episomal plasmids, minicircles) and specific delivery vehicles is improving very fast.

During my tenure in NCI (1980-2008) I mostly worked to discover cancer genes. Based on some novel findings I suggested several novel treatments (vaccines, antibodies, and already approved drugs for other diseases (glaucoma) to slow down tumor growth. In the years 2006-2008 I proposed a new approach how to treat and cure cancer with

combined gene therapy (CGTC). Like my previous proposals this one was also rejected and I was forced to retire in 2008. A short description follows.

Combined Gene Therapy of Cancer Directed at Tumor Stem Cells and Patients Hematopoietic Stem Cells

Michael I. Lerman, M.D., Ph.D. (2006-2010)

The essence of my proposal is to use two known tumor suppressor genes expressed from episomal vectors: one delivered to cancer stem cells to suppress tumor growth, the other delivered to patients hematopoietic stem cells to boost the immune system to attack and destroy the tumor.

This cure program applies to all forms of cancer and all patients regardless of their genetic background, gender and age. It totally departs from the prevailing dogma that requires specific therapeutics with "targeted" drugs for each type of cancer, to be tailored to each individual tumor and patient background ("personalized treatment").

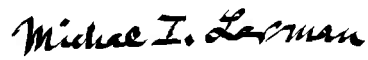
I know the genes (VHL and FUSI) and how to deliver and express them in the right cells.

This is a Manhattan type project but the cost will be thousand times less.

In the very near future, verily, humans may be genetically modified to carry an additional functional copy of the highly conserved gene, Fus1/Tusc2. I classify it as a Janus (two-faced) type gene that is most suited for prevention and gene therapy of cancer. On one hand it's a classical tumor suppressor gene (TSG) on the other it's a powerful regulator of the immune system. Over-expression of this gene will suppress and prevent tumor formation and boost the immune system leading to overproduction of hematopoietic stem cells (HSC) and most effector cells thus activating the immune attack on tumor cells. In addition, individuals with an extra functional copy of the gene will be resistant to immune diseases, and infectious diseases including HIV.

Sincerely,

Michael I Lerman



Tue 11/1/2011 12:41 PM
Re: National Bioeconomy Blueprint

Dear Tom,

Our recent dialog about the National Bioeconomy Blueprint prompted a presentation, attached, on how ExQor believes it can facilitate this significant effort. We will be in Washington D.C. Nov. 12 -15 attending a medical conference. If you have the time we can discuss this further.

Regards,

Franco Vitaliano
President & CEO
ExQor Technologies, Inc.

ExQoria

The Cognitive Cloud

ExQor Technologies, Inc.

Boston MA USA

About ExQor

ExQor Technologies, Inc. is a multi-disciplinary company, founded in February 2004 in Boston MA, USA.

ExQor is the only company that has fully embraced the National Science Foundation's principles of "Converging Technologies for Improving Human Performance" by synergistically unifying the multidisciplinary field known as ***NBIC***.

ExQor has developed an integrative product approach that unifies **N**anotechnology, **B**iotechnology (via nano-medicine), **I**T (via the Web, Internet, mobile communications), and **C**ognitive science (via cognitive pipelines & clouds).

ExQor has developed a unique new model of human cognition based on the brain's dynamic biological and developmental processes, from infancy to adulthood. It is not AI, nor a neural net. It is something totally new in cognitive science.

ExQor's breakthrough in cognitive science also led to a major biomedical innovation in understanding the central nervous system and how to treat its diseases and disorders.

In one business role, ExQor is developing innovative new large molecule drugs for treating CNS cancer, and also for enhancing CNS neuroprotection and neuroregeneration for treating neurodegenerative diseases, stroke, and traumatic brain injury.

Some of the biomedical research is being done under non-exclusive license at Harvard Medical School (McLean Hospital), and funded by the NIH, NIDA, NARSAD, private foundations, and other funding sources.

ExQor's bio-nanotechnology is broadly protected under multiple issued patents, with additional patents pending in the US and elsewhere in the world.

About ExQor

Franco Vitaliano, President and CEO and ExQor co-founder and co-patents holder, was formerly President & CEO of VXM Technologies, a Boston-based firm that specialized in advanced bio-nanomaterials and novel, network parallel and massively parallel computer architectures for extremely high performance systems.

These systems were based on his more than two decades of work in developing advanced models of human neuro-biosystems and modeling proteins in the brain. VXM's clients included General Motors, Ford, Chrysler, GTE, the U.S. Air Force, the U.S. Navy, MITRE, the NSA, General Dynamics, Sandia National Labs, Argonne National Labs, and the DOT, among other major clients.

At ExQor he conceived and developed the company's unique and extensive bio-nanotechnologies and also formulated its global business strategy.

He also has extensive expertise in formulating global IP/patent strategies, and was primarily responsible for the conceptualization, technical drafting, and successful defense and approval for all of ExQor's patents.

He has served as an expert in bio-nanotechnology at the President's Innovation and Technology Advisory Committee (The White House), and on DOD conferences.

Gordana Vitaliano, M.D., Vice President and ExQor co-founder and co-patents holder, was formerly the Director of the Nanomedicine Lab for Neuroscience at Caritas St. Elizabeth's Medical Center in Boston MA.

She is an NIH grant recipient and sits on NIH review panels for bio-behavioral science. She emigrated from Serbia to the U.S. in 1991 (where she received her medical degree at Belgrade University) when she won a highly prestigious NIH Fogarty Fellowship.

She is currently employed at McLean Hospital (Harvard Medical School) in Belmont MA, where she is designing bio-nanotechnology with the potential to become a powerful tool in medicine, and in the future may lead to the development of diagnostic tools, targeted delivery systems and cellular repair platforms for the CNS.

This nanotechnology research work, for which she has received 3rd party grant support after extensive scientific panel review, involves utilizing ExQor's patented bio-nanotechnology for advanced CNS applications in medical imaging and drug delivery. The work is being done under a non-exclusive license from ExQor.

She has served as an expert in bio-nanotechnology at the President's Innovation and Technology Advisory Committee (The White House), on NIH review panels and on NIDA and DOD conferences.

***ExQori*Δ** Transforms The Cloud

- ExQoriΔ is a new, unique kind of software entity.
- ExQoriΔ transforms conventional clouds.
  - ***It is a Cognitive Cloud***
- Strongly personalized, highly dynamic, contextualized user experience.
- The ExQoriΔ Cognitive Cloud *knows you*, is always there for you.
  - ***Quantum leap beyond iPhone's Siri***
- Novel, Multidimensional, Secure Platform.
- Compelling Customer Attraction, Strong Growth and Retention.

***ExQori*Δ Transforms The Cloud**

Self-knowledge — The ExQoriΔ Cloud can identify its purpose and understand its internal functions.

Perception — The ExQoriΔ Cloud has the ability to self-recognize, interpret, and understand highly complex inputs.

Reasoning — The ExQoriΔ Cloud is capable of making intelligent, autonomous decisions based on its own perception of the environment and carries out tasks to successful completion by using its own initiative.

Cognition — The ExQoriΔ Cloud's intellectual processes include all aspects of knowing, such as awareness, perception, reasoning, and judgment.

***ExQori*Δ** Transforms The Cloud

- Robust, Secure, Deep Platform Architecture.
- ExQoriΔ transforms heterogeneous, multipoint services, data, content, and devices into a globally unified, self-aware, *cognitive* cloud.
- Cognitively correlates global user requests, experiences, relationships, requirements.
- Injects its own “insight” into end user activities, contextualizes user experiences.
- Highly dynamic, customizable and personalized user experience.
- Transforms people’s relationships with the Web, Internet, and each other.
- Allows users to cognitively search, share, and correlate data, content, life experiences on a global scale.

***ExQori*Δ Transforms The Cloud**

- ExQoriΔ cognitively uses and examines information from all available global data.
- ExQoriΔ automatically formulates complex queries and actions.
- Intelligently real time iterates across heterogeneous data elements and sources.
- Alters its internal operations based on its "outside" observations or interpretations, categorizing new data based on prior results.
- It deciphers incomplete or inaccurate data by considering it in conjunction with related information and judgment,
  - *A human cognitive function replicated in ExQoriΔ's algorithms.*

The Engine That Powers The ExQori∆ Cloud:

ExQor's Cognitive Internet Pipeline

- Intelligently, autonomously does the work.
- Puts results into highly individualized user context.
- Automatically stays abreast, intelligently examines continually changing data and user requirements.

ExQor Cognitive Pipeline Engine

- Employs and integrates multiple types of discovery strategies.
- Performs highly complex, integrative, iterative searches across disparate data.
- Continually refines its operations.
- Delivers highly individualized, pertinent, real time results based on its growing self-knowledge, perception, reasoning and cognitive faculties.

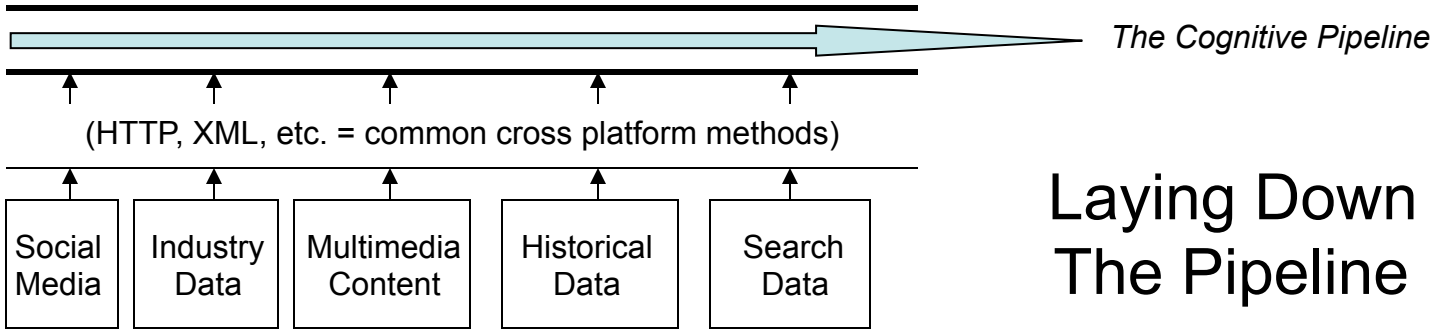
ExQor's Cognitive Pipeline Engine

- A new type of software platform for the Internet, Web, mobile telecommunications, social media, & more.
- Uses Internet and Web standards to globally integrate data, systems, social media, and devices.
- Non-disruptive overlay to existing data.
- Allows cognitive exchange of information between data types without requiring them to be translated into same format.
- High throughput.

- Very proactive.
- Highly interactive, cognitive correlation of real time events, data, social interactions.
- Cognitively puts all available elements into global or highly individualized context.
- Enables highly personalized, contextualized, secure services.

ExQor's Cognitive Pipeline Architecture

- A new information processing paradigm that can handle vast quantities of heterogeneous data in real time.
- Allows seamless integration of the multitude of point applications that have sprung up and captures multi-workflows for industrial and commercial analysis, design, deployment, or highly personalized consumer use.
- Internet pipelining is a new computational approach to managing the exchange of information among various data in order to maximize both the flexibility for addressing unexpected data types and the potential for introducing creative & cognitive insight.



Laying Down The Pipeline

ExQor's Cognitive Pipeline Engine

Handles the hard questions:

What does it all mean?

How do I find out?

Do I have to do all the work?

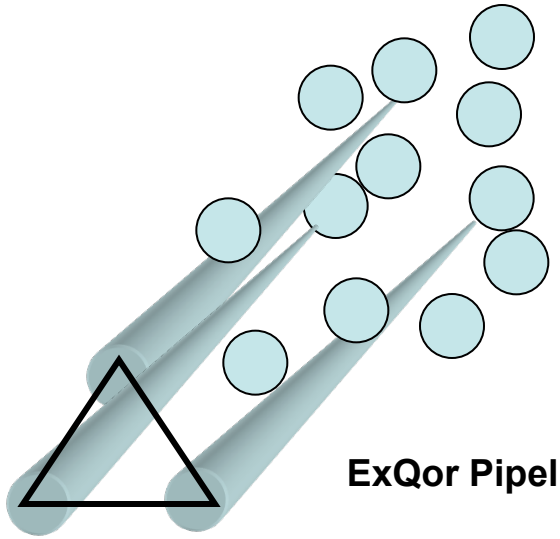
Will it understand my problem?

Who puts results into a meaningful context?

How do I use the results?

Who else should I share them with?

How do I stay up to date in real time?



ExQor Pipeline Engine

Finding & discerning results, patterns, meaning, putting them into cognitive context, staying abreast in real time.

HealthCare.gov

ExQoriΔ

Transforming All Into One

ExQoriΔ Cognitive Cloud

- Secure
- Integrated
- Analyzed
- Contextualized
- Customized
- Real Time

Self-Aware

ExQor Cognitive Pipeline

(XML, etc., + HTTP = common cross platform methods)

Provider Data | Industry Data | Scientific Data | Financial Data | Medical Data | Patient Data | Government Data

ExQoriΔ

The Cognitive Cloud

Only From

ExQor Technologies, Inc.
Four Longfellow Place, Suite 2105
Boston MA 02114-2818 USA

Tel 617 742 4422
Contact: Franco Vitaliano
e-mail: francov@exqor.com

Sent: Fri 11/4/2011 12:19 PM

Subject: Request for Information: Building A 21st Century Bioeconomy

Creating a 21st century bioeconomy depends on training excellent bench scientists and scientist/entrepreneurs. Biomedical research is a complex enterprise that requires scientists to engage in a variety of fields outside of bench research including economic, political, legal, and social arenas. However, the training graduate students and postdoctoral researchers (postdocs) receive is not sufficient to ensure success in the variety of careers available to them. This is a potential hindrance to creating a 21st century bioeconomy. Therefore, reorganization of the training programs for graduate students and postdocs is the most important topic for the Office of Science and Technology Policy to focus on because the type and quality of training of new scientists will shape the national scientific endeavor for decades.

Collaboration between academic scientists and biotechnology companies is essential to efficiently translate discoveries from the bench to the marketplace. The establishment of the National Center for Advancing Translational Sciences and the Cures Acceleration Network shows the commitment of the NIH to finding treatments and cures for disease. These programs will discover important new compounds, materials, and techniques. In order to bring these products to the market in the quickest, most efficient, and safest manner possible, graduate student and postdoctoral training should educate scientist/entrepreneurs in technology transfer and the process of commercializing important biomedical products.

To support the pipeline that brings new treatments and technologies to market, we must expand the breath of careers available to graduate students and postdocs. For example, training scientists as political advocates will allow them to make the case to legislators regarding predictable increases in NIH funding. NIH funding creates jobs, increases economic output, and is an essential aspect of the 21st century bioeconomy. Additionally, arming graduate students and postdocs with the most effective educational techniques will improve K-12 and college curricula. Training scientists as communicators will let them effectively convey the facts, goals, and impacts of biomedical research to non-scientists and the media. Finally, scientist/lawyers who understand the significance of biomedical innovation will ensure this work is safeguarded from a legal standpoint.

I have two recommendations to improve the career training of graduate students and postdocs.

A. **Diversify graduate student training through establishment of programs that facilitate collaboration between biomedical and non-biomedical departments.**

Colleges and universities contain a large number of highly educated people who are generally interested in disseminating knowledge. Collaboration between individuals in

different departments has led to groundbreaking discoveries and technologies. For example, the recent expansion of the bioinformatics and biophysics fields is due, in part, to improved collaboration between biomedical research departments and computer science and physics departments. The success of graduate students in these fields can also be partially attributed to acquiring a broad skill set encompassing multiple areas.

The OSTP should encourage expanded collaboration between biomedical research departments and non-science departments in order to broaden the skill set of graduate students. This could be achieved through a college- or university-wide, graduate student exchange program. This program would serve two goals: First, biomedical graduate students could intern in the business or communications departments, for example, to learn skills that will help them run a successful lab, start a biotech company, or advocate on behalf of biomedical research to the government, media, or public. Second, graduate students from non-science departments could gain lab experience, gain a better understanding of scientific research, and become ambassadors for biomedical research.

While internships for biomedical graduate students in non-science departments are rare, the structure for such a program is already present in nearly every Ph.D. granting program in the United States. Almost all graduate students are required to be a teaching assistant as part of the requirement for attaining their degree. Teaching assistantships are designed to give graduate students classroom experience, and graduate students are expected to spend 10-15 hours each week to prepare for their classes. The graduate student exchange internship could be set up with similar parameters.

Entry into the internship for biomedical students could require a detailed application explaining their goals for entering this program and a proposal for their work during the internship that should show a certain degree of relevance to their own research. These proposals could be vetted by a panel consisting of faculty members from each department involved in the exchange. Entry into the internship for graduate students from non-science departments would follow a similar path, including a research proposal that is somehow relevant to their work in their own department.

Internships in the graduate student exchange program could work on a basis similar to teaching assistantships. Biomedical graduate students could spend 10-15 hours per week working on their projects with faculty members from other departments while learning the skills outlined in their initial proposal. Similarly, graduate students from non-science departments would be expected to spend 10-15 hours per week in a lab working on their proposed research. The length of the internship would depend on the departments involved, but could range from one semester to several years.

The benefits of such graduate student exchange programs would be immediate and profound. By requiring that internship projects be somehow related to their own research, graduate students will be forced to consider their thesis work in a different light. For example, graduate students interested in the process of commercializing and marketing biotechnology would be forced to think of the commercial and social values of

their work, in addition to the scientific value. The benefits of this alternative approach to their thesis work would offer new insights and potentially hasten the students' graduation. Graduate students who teach during their time as a student are able to better formulate hypotheses and design experiments than students who did not teach (Feldon et al., *Science* 2011). Enrollment in the internships proposed here should have a similar effect since they ask the students to reevaluate their thesis work and address problems with different techniques and thought processes.

The inclusion of graduate students from non-science departments in the graduate student exchange program is critical. While they may not grasp the nuanced scientific concepts tested in every experiment, they are smart, motivated individuals who are eager to learn and can serve as ambassadors for biomedical research once they finish the internship. This internship is an opportunity to improve science literacy among non-scientists and improve the public perception and understanding of biomedical research.

The role of the NIH in the graduate student exchange programs would be to fund pilot programs at select universities, follow the progress of students through these programs, and assess the students' and professors' opinions of the program. At the end of a 5-year trial period, the NIH could issue recommendations and offer financial support for the establishment of other programs around the country.

B. **Initiate a professional development grant program for postdoctoral scholars**.

The main source of extramural funding for postdocs is the National Research Service Award (NRSA). This is a highly successful program that awards grants on the basis of the scientific merit of proposed research and prior achievement. The NRSA program could serve as a model for a granting program that would improve postdoc professional development.

The application process for professional development grants would be similar to the current NRSA format in which postdocs make strong arguments for the importance of funding their research. In addition, applications for these new awards would include a section for the postdoc to propose a program of study with an advisor in another department or outside of the college or university altogether. Similarly, the professional development advisor would write a letter explaining the value of the postdoc's work to the department or organization. Professional development grants would be evaluated by a panel of scientists, similar to the NRSA, while considering the feasibility of the proposed skill development program.

Postdocs receiving a professional development grant would be expected to fulfill their lab obligations and make progress in their scientific endeavors. Training with their non-science advisor would take 10-15 hours of the postdoc's time each week. To optimize postdoc professional development, the NIH should limit professional development grants to 1 year. This would force postdocs and their scientific and outside advisors to develop a plan that allows postdocs to broaden their skill sets in anticipation of their next career steps without sacrificing the progress of their science.

Professional development grants would be appropriate for postdocs with a variety of career goals. For example, postdocs interested in establishing their own labs could learn managerial skills by interning with a management consulting firm. Alternatively, a postdoc studying lung cancer and interested in public relations might propose to work with a communications department faculty member or a local chapter of the American Lung Association. Finally, a postdoc interested in technology commercialization could intern in the college or university's technology transfer office during the grant period.

To measure the success of professional development grants, the NIH should analyze a variety of parameters over a 5-year trial period. First, the number and quality of applicants will serve as an indicator of the popularity and necessity of professional development grants for postdocs. Second, the scientific progress of postdocs during the granting period should be considered. The purpose of a professional development grant is to expand a postdoc's skill set while having a minimal impact on his or her lab productivity. Third, the postdoc and his or her scientific and outside advisors for the granting period should submit reviews of the professional development program to determine the usefulness of the experience. Additional metrics that assess the success and efficiency of professional development grants for postdocs could be considered as well.

Funding professional development grants would not require an increase in the budget allocation for the NIH. Rather, the NIH could convert a small fraction of NRSAs into 1-year professional development grants. Converting 2- to 3-year NRSA grants into 1-year professional development grants could fund 2 to 3 times as many postdocs as an NRSA in the same amount of time. Similar to the NRSA, the professional development grant would fund the postdoc's salary with a small allowance for lab supplies and travel to meetings.

Professional development is essential for postdocs to achieve their career goals regardless of the path they choose. However, scientific success is often a requirement for entry into any science-related field whether it is in academia, law, government, or business. Therefore, professional development grants would allow a large number of postdocs to receive NIH funding, accomplish their scientific goals, and improve their chances of success in their chosen career path.

To the Science and Technology Policy Office:

In response to RFI:Building a 21st Century Bioeconomy

Question (5) The toughest money to get is the bridge between research findings arising at university and research institutes that produce embryonic ideas and inventions and conventional investment. The SBIR and STTR programs were to address this gap, however in my experience too little risk is associated with the choice of proposals that receive support. Possessing data that provides a reasonable assurance of success in Phase I exploratory undertaking, seems a poor criteria for funding and places many worthy ideas and proposals in a Catch-22 situation beyond the reach of funding.

Question (6). The SBIR program has been artificially constrained by limiting the amounts that can go to venture backed companies. I don't believe there should be limits or set-asides for any specific group. If science and technology are to be translated into products benefiting the public, the best proposals should receive funding regardless of their small business origin, structure or existing support origins of the submitting organization. Why would any program want to support less than the absolute best ideas? A venture-backed company focused upon their core asset should be able to explore additional areas by leveraging their time and talent in areas deemed too risky for additional investment by the venture community. This has relevance to question (8).

Question (9) Few institutions take the time include in doctoral training even minimal exposure to the corporate world or business thinking. I have personally taught courses where doctoral students and post-doctoral students attend because they are curious or frustrated in their laboratory-based careers, however the current academic environment doesn't appear to prepare them for anything beyond a bench-focused career in science. Exposure in graduate school to the business of science in a formal way could enhance their experience and prepare students to make informed career choices proactively.

Question (12) If students are to be successful entrepreneurs they must be exposed early to the opportunity. It is unlikely that one would produce a scientist without teaching them how to write a successful grant. Yet, unless one's mentors have experience in the area, it there is unlikely to be exposure. Why would formal exposure to the workings of business from technology development fundamentals to start up company workings to large industry function not be a part of the educational preparation received to prepare a well-rounded individual ready to take their place in society? Appropriate programs or curriculum could be developed to achieve these ends without distracting unduly from scientific pursuits.

Thank you for the opportunity to provide input.

John Perchorowicz, Ph.D.

President

Triage Masters LLC

Complementing the Genome with the Exposome: Mapping Environmental Exposures

Complex diseases are known to have both genetic and environmental components. Low-level and prevalent environmental exposures may contribute substantially to the burden of common complex disease (Hemminki et al, 2006, Gibson, 2008). Characterization of susceptibility is rapidly advancing through application of microarray technology for genotyping and investment in large genome-wide association (GWA) studies (McCarthy et al, 2008). Epidemiologists are now facing the challenges associated with interpreting this massive amount of genomic variation data for understanding etiology of complex environmental disease. Calls for tools to characterize and unravel interacting genetic and environmental factors have begun (Collins, 2006; Manolio and Collins, 2007).

Despite these calls, accurate assessment of environmental exposures remains an outstanding and largely unmet challenge; characterization of exposure remains primitive and resources to improve the scientific basis of exposure assessment are limited or nonexistent. This raises the question as to whether fundamental knowledge about genetics will improve understanding of disease etiology at the population level (Wild, 2005). One side of the gene-environment equation continues to be refined while the other remains subject to crude characterization. Due to the complex nature of the human system, predictions of potential health risks associated with environmental exposures will be limited by the least resolved or least understood component of the system. By focusing resources exclusively on characterizing genetic susceptibility we compromise the ability to fully realize benefits of the genome and of large GWA (genome wide association) studies. Just as a new generation of scientific tools has provided the ability to efficiently assess genetic susceptibility, there is a critical need to develop methods for characterizing environmental exposures at biologically-relevant resolution.

Understanding the contribution of environmental factors to disease susceptibility will require a more comprehensive view of exposure and biological response than has traditionally been applied. Wild (2005) has proposed the need for a "step change" in exposure assessment and has articulated a vision for exposure measurement calling for an "exposome," or measurement of the life-course of environmental exposures to provide the evidence base for public health decisions to address environmental health. Wild and others (e.g., Wild 2009) discuss the potential of emerging technologies to provide this new generation of exposure information. In their guest editorial in EHP, Smith and Rappaport (2009) argue that if we expect to have any success at identifying the contribution of environmental factors on chronic diseases, we must develop 21st-century tools to measure exposure levels in human populations and to quantify the exposome.

This past February, the National Academies of Science organized a workshop titled "The Exposome: A Powerful Approach for Evaluating Environmental Exposures and Their Influences on Human Disease" to examine the concept of the exposome and its importance to the etiology of human diseases. A strategy for utilizing banked samples from large birth cohort studies to develop, evaluate and pilot advanced biomarkers to map the Exposome was presented.

Mapping the Exposome is a grand scientific challenge of national and international importance. The Exposome is required to measure exposure and to elucidate the impact of environment on biology and on disease. Without investment in advanced technology to measure and diagnose exposures, the potential of our national investment in the genome, in genetic epidemiology and in personalized medicine cannot be realized.

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Mon 11/14/2011 1:07 PM

My comments are addressed to the RFI listed as:
http://www.gpo.gov/fdsys/pkg/FR-2011-10-11/pdf/2011-26088.pdf

Grand Challenges:

1. Rational basis for polypharmacy. HIV/AIDS needed a therapy based on simultaneous delivery of a cocktail of drugs, because of the virus' capacity for rapid evolution. Cancer presents the same problem. Successful treatments have evolved empirically using a cocktail of low specificity toxic drugs. The reductionist approach favored by molecular biologists, like myself, have focused on single, highly specific inhibitors, such as tyrosine kinase inhibitors. Efficacy is good but remission is almost universal. New developments in mammalian cell genetics, such as synthetic lethality, allows a rational approach to polypharmacy that will allow the use of a cocktail of drugs but each with high specificity.
2. Molecular signatures of disease. New developments, for example in using DNA sequencing to measure protein synthetic rates, allow the researcher to see even a 20% change in a protein marker in response to a disease, thus laying the foundation for protein based, molecular diagnosis of most if not all the major human diseases. Although this is especially needed for Alzheimer's disease, it can be of value across disease categories. Since NIH is structured to focus on diseases, such a pan-disease effort to develop molecular signatures may need a restructuring equivalent to that needed for the Human Genome Project.
3. DNA sequencing for PHENOTYPIC analysis. Much current focus is on the $1,000 genome. Our genome certainly contributes to our disease proclivities but our environment plays at least as significant a role. We need a greater emphasis on using new DNA sequencing capacity to detect pathogens in our body and to characterize our microbiome more extensively.

Research and development:

1. Align research investment more with medical need. Kidney disease and its treatment with dialysis, for example, is a major financial burden on our health care system. Funding for innovations that can replace our cumbersome and expensive dialysis systems is almost non-existent. Alzheimer's is a growing threat to our economy yet we invest more in HIV/AIDs than in Alzheimer's.
2. Support Research on Cost-reducing technologies. Current NIH funding supports improvements in the quality of health care. There is no funding category that supports technological advances that might make health care more accessible by reducing its cost. The private sector has little interest in such developments; for our continued economic viability as a nation, it is essential.
3. Reduce redundancies. A common criticism of NIH from outsiders is that many labs may be funded to do the same research. In times of austerity, reviewers should be alerted to the existence of other grants funding essentially the same work when setting funding priorities.

Lab to Market:

1. Modify NIH Funding Requests. Grant applications currently require the writer to define what diversity programs exist in their university. This has been a very successful strategy. If the NIH were to ask what the applying institution is doing to foster entrepreneurship, and how successful those steps have been, US universities would become hot-beds of entrepreneurship in a couple of years!
2. Support Academic Generalists. The current system favors specialization while innovations come from cross-disciplinary interactions. Academic institutions do not recruit generalists, those who are talented at assimilating vast amounts of information and seeing unexpected connections. They should.
3. University-associated incubators. Close association of budding entrepreneurs with the mother campus is of crucial importance in the first difficult year or two of company formation. Conversion of under-utilized university space to small incubator labs should be encouraged, for example, by removing legal and policy objections to commercial work on university campuses.

4. Small Business Grants. These are the life blood of lean start-ups. The money is so valuable that the government should resist pressures from the National Venture Association to use them as non-dilutive funding. If tensions exist between politicians who favor the creation of Mom-and-Pop retail stores in middle America and those who want to use such grants to stimulate innovation then a reconciliation effort should be mounted. These are the crown jewels of the NIH in our opinion.
5. Seed funding. Money for life science start-ups in notorious hard to find. One possibility is to allow research universities to apply for one-time loans with which to fund start-ups, with the idea that they should generate enough income from their investments that their program be self-sustaining.

Regulatory Barriers and Re-imbursement policies

1. Diagnostic devices. Modern treatment is moving rapidly towards companion diagnostics and, hopefully, molecular diagnoses of disease. Unfortunately venture funding for such areas is minimal, because of the poor return and the challenging regulatory environment for diagnostics. To improve the situation, the FDA should endorse the use in America of any diagnostic approved in Europe.
2. User driven innovation. The Defense department specifies the characteristics of a weapon it wants to be developed and may give a price it is willing to pay. The Government could revolutionize the industry if it would announce medical improvements it was seeking, acceptable side effect to benefit ratios and the price it would pay for a successful product or procedure.

Public-Private partnerships.

1. Science Hotels. The turmoil in the R&D divisions of major pharmaceutical firms is challenging them to seek inexpensive and effective alternatives. One possibility is to have satellites of companies locate next to major research universities in science hotels so that company and university scientists can work together to solve a major health problem. When the problem is solved the company would leave. Tax breaks might encourage companies to engage in such partnerships.
2. Regulatory Science Think-tanks. Objective, impartial entities are required to assess the value of regulatory processes and whether one regulation should be replaced by a more effective one. Creation of a National Regulatory Think-tank, independent of political or industry pressure, devoted to informed analysis of regulatory policy could be a national asset.

Regis B. Kelly, Ph.D.
Director,
California Institute for Quantitative Biosciences (QB3) Professor, Dept. of Biochemistry & Biophysics, UCSF

Ideas for Bioeconomy – Aquaculture Thu 11/17/2011 3:49 PM

FAO recently announced that aquaculture (the controlled farming of aquatic species) was the world's fastest growing sector of animal protein production. There is a reason for this. Most of the world realizes that seafood is a high quality and concentrated protein source to feed their people, and aquaculture has a lot of promise and growth potential. Many countries are investing heavily in aquaculture development, except the US which currently appears content with simply importing the vast majority of its seafood. The US imports 85% of its seafood accounting for a $10 billion trade deficit. However, the US is rolling dice with its future. As seafood demands grow worldwide, there will be increasing concerns about the supply, safety, and sustainability of seafood in the US. For instance, China, the world's largest producer of aquacultured products and once the world's largest exporter or shrimp, is predicted by 2013, to become a net importer of shrimp because of the projected population increase and the increasing demand for seafood as incomes rise in that country. This will cause reduced supply in the US as other producing countries divert their exports to China. Reductions in quality in the US will naturally occur as the US scampers to fill its demands with whatever is left over. Increased price, lowered quality, and less choice (variety) is what the US can expect in the very near future. Already, there are concerns for the safety of our imported seafood by unsustainable practices that occur in other countries from which we already import heavily. Antibiotics, melamine, salmonella are just a few examples. The US wild capture fisheries simply cannot supply the demands for seafood in the US and stocks are already fished to maximum yield. We cannot get more fish out of the oceans. Aquaculture is the only way for the US to meet current demands and fulfill future protein needs of its people as protein sources become increasingly limited through a rapidly growing world population.

The US should not wait for an inevitable "seafood crisis" in this country. The US should be proactive and invest in programs that support the development of aquaculture nationwide now. The US should not be dependent on foreign supplies and market forces it cannot control. Currently, the US lags sorely behind other countries who have established and well -funded national programs for aquaculture. Part of the problem has been that no one agency has taken the lead in aquaculture development in the US. At last year's Aquaculture America conference in New Orleans, it was indicated that approximately 13 federal agencies are involved at some level with aquaculture. This is wasteful bureaucracy, creates an myriad of conflicting regulations, and frustrates development of the industry and jobs creation. The National Marine Fisheries Service under NOAA, for instance, has indicated that development of aquaculture in the US is the only way to create jobs in the seafood sector and increase the supply of seafood in this country. Yet the NMFS budget for aquaculture is $8 million/year for the entire country.

One strategy is to establish a well-defined National Aquaculture Agency in the US that has the responsibility to coordinate, develop, and promote aquaculture in the US. This agency would be well-funded to help establish policy and clear guidelines, rules, and regulations for promoting aquaculture. It would also be the primary funding arm for research and development projects. Existing monies can be shifted from unsustainable and unpopular programs, and programs that just collect information rather than actually creating something. A budget of $50 million per year would be targeted. Yet government should also promote industry buy-in a co-investment of this effort so both the agency and industry are vested.

One idea in which to accomplish this buy-in is by creating public-private partnerships in establishing research and development centers in strategic areas of the country to help support commercial investment in aquaculture. Government funded research centers targeting species and technologies specific for the regions are one of the best, most vested ways to proceed that would have immediate

success and impact, and which has a successful track-record in other countries. These centers would provide both the research and logistical support need to spur investment and success. For instance, the establishment of broodstock animals often takes years for a commercial company to develop, and is usually a large, upfront cost for a nascent company. Several years of time, money, and risk would be expended until the animals produce eggs without cash flow into the investment. This frustrates investment and makes for a difficult business model. The federal government can help industry by absorbing these upfront costs by establishing broodstock centers of targeted, regional species (targeted by industry) to supply eggs and fingerlings (juvenile fish) for upcoming farms. Bypassing the expense of establishing broodstock anew would allow farmers to have almost immediate cash flow into their operations by obtain fingerlings to stock into growout, and establish themselves in the marketplace. This cashflow would then allow farmers to invest the time and money in developing their own broodstock capabilities. Once industry establishes broodstock capabilities after already having established themselves as a viable business, the Center would then transition from that species onto the next species for development.

Thank you for considering these thoughts.

Best regards,

Anthony C. Ostrowski, Ph.D.
President
Oceanic Institute
www.oceanicinstitute.org

Thu 11/17/2011 10:40 PM

"Addressing Rural Hawai'i's Need for Energy & Food Security".

Aloha,

We (the Company) are in the process of planning a "BioEnergy Hub" in the Rural District of North Kohala on the Big Island of Hawai'i. We are projecting a near-shore Wave Energy Conversion (WEC) Platform providing: power and sea water to an onshore integrated Mari-culture Cluster; an Algae PhotoBioReactor (PBR) Plant and a Shellfish Hatchery and Culture System, which will complete the development of the Ocean's resources: (Phase I).

To this end: the Company has recently received a USDA-RURAL REAP Grant to conduct a WEC Feasibility Study at the proposed site. We (the Company) are seeking matching funds to deploy an Acoustic Doppler Current Profiler (ADCP) array to determine feasibility.

Favorable results will launch Phase II of the Project Plan; an Anaerobic Waste to Energy (AD-WtE) Plant, integrated with the PBR Plant, generating Electricity, BioFuels, Fresh Water, providing the PBR Plant with: CO2, Electricity, Fresh water, Heating & Cooling to operate the Plant. Effluents and Solids from the WtE Plant valuable sources of Micronized Nutrients for Aquaculture & Agriculture use. Phase II will also develop fresh water Aquaculture of: Microalgaes in the PBR, Finfish Hatchery and Grow-out, Aquaponics, and BioDynamic Agriculture practices.

Additional sources of Alternative Energy available with the addition of Solar & Wind; completing a "BioEnergy Hub."

To this end: We (the Company) have formed Partnerships (NDAs-Strategic Alliances) with the following Developers of WtE technology and Engineering:

Omnigreen Renewables LLC, Wai'anae Hawaii (OGR); Clean World Partners LLC, (CWP)UC-Davis; Essential Consulting Oregon LLC (ECO); 3d-Innovations LLC-HTDC, Oahu, Hawai'i; Sea Engineering, Inc. (SEA), Oahu, Hawai'i.

We invite your interest, Power Point document available by request.

Proprietary Disclosure of Technology, IP, and know-how available with a NDA.

Best Regards,

Frank 'Palani' Cipriani

BioFarms Hawaii LLC

www.biofarmshawaii.com

"Non Escribe, Non Dictum": "Not Written, Never Said."

The Landscape

Not only an economic engine, a robust U.S. medical technology industry produces life-saving, life-enhancing treatments and cures for patients. Although the U.S. still dominates the global market, U.S. investment in R&D as a percentage of GDP is presently declining while other countries, including China, Brazil, and India, have increased their investment in this area. Within 10 years, China is expected to be on a par with the U.S. in R&D investment as a percentage of GDP [1]. Due in part to a cumbersome regulatory system (America's regulatory approval times rank 7th out of our top nine competitor nations), U.S.-based medical technology giants are increasingly looking abroad to capitalize on investing where the growth is most promising. For example, GE is moving its X-ray leadership team from the U.S. to China, and Siemens has manufactured imaging and ultrasound systems in India for more than 50 years. China's medical device market is expected to increase by 15% annually during the next five years to $43 billion by 2019; India's will grow by 23% during the same time to $11 billion annually [2]. Furthermore, emerging market countries are quickly taking the lead in developing lean, frugal, and reverse innovation that simplifies existing devices and processes. Therefore, maintaining U.S. dominance in the $350 billion global medical device industry will require a national response to product development, which will have significant impact not only on innovation and retaining and creating high-wage, high skill jobs, but also healthcare costs.

Value-driven Engineering

The Austen BioInnovation Institute in Akron (ABIA) led an academic, industry, and government collaboration to explore the effect of value-driven engineering (VdE) on the nation's global competitiveness. The *Safe Haven Summit on Value-Driven Engineering and U.S. Global Competitiveness* was held on March 10 and 11, 2011. Both industry and academic participants from institutions such as SEMATECH, Medtronic, Stanford and MIT, as well as thought leaders from the Ewing Marion Kauffman Foundation were in attendance. As a result of the Summit, a White Paper was written in which modifications in regulatory and reimbursement practices and recommendations for training the next generation of innovators were described [3]. In addition, a focus on Clinical Utility and Reduced Complexity and Healthcare System Cost reduction from design through development and manufacturing of medical devices and processes was included. This has been expressed in the following Value Equation:

$$\text{Value} = f\left(\frac{\text{Clinical Utility}}{\text{Complexity} \times \text{Cost}}\right)$$

"Clinical Utility" and "Reduced Complexity" (i.e., the time and effort required to perform a procedure correctly) are considered from the perspective of the end-user, and "Cost" is evaluated systemically. In healthcare, VdE represents an approach to developing new products that conform to the following principles:

1. Assurance of Quality- performance and delivery are never sacrificed for the sake of a "cheaper" or "less costly" version of a product or process;
2. Clinical utility driven by patient-centricity in demand, design, use, and function;
3. Reduced complexity in product design; and
4. Demonstrated cost savings and cost efficiency across the health system.

VdE is distinct from the value engineering principles employed by the Department of Defense's procurement office. As described in Public Law 104-106, Section 4306 [4], which requires the use of value engineering procedures and processes by each executive agency, value engineering analyzes the "functions of a program, project, system, product, item of equipment, building, facility, service, or supply of an executive agency, performed by qualified agency or contractor personnel, directed at improving performance, reliability, quality, safety, and life cycle costs". In value engineering, value is defined as the ratio of function to life cycle cost. VdE is distinct from value engineering as it defines value is a function of clinical utility and complexity at the end-user as well as cost to the overall system. Thus, VdE offers tremendous potential to bolster U.S. global competitiveness while concomitantly serving as a tool to bring healthcare costs in line with quality outcomes.

The following recommendations to advance VdE will be discussed individually:

1. Launch PAVE: Platform to Advance Value-driven Engineering
2. Adopt a regulatory framework to advance VdE product development
3. Train and Inspire the Next Generation of Engineers

Launch PAVE: Platform to Advance Value-driven Engineering (in response to questions 2 and 16)

The Platform to Advance Value-driven Engineering (PAVE) includes funding mechanisms, regulatory incentives, supports for cross sectors investments, and educational leadership that incorporates the principles of VdE and deploys the Value Equation as a core driver and test for VdE device product innovation. The PAVE framework is founded on the following pillars:

1. Demonstrated value, employing the Value Equation;
2. Patient-centricity, with community and customer engagement in product demand and design;
3. **Public-private engagement and investment, dependent upon innovative and budget-sensitive federal funding mechanisms, cross sector human and financial capital contributions**, **and collaboration across disciplines, bringing engineering into a close integrated working relationship with biology, medicine, clinical application and health system performance**; and
4. Educational focus requiring the adoption of new academic programs that train today and tomorrow's cadre of VdE engineers.

RECOMMENDATIONS:

- Launch and manage PAVE as a program of the Administration with the authority and capacity to assure cross-departmental coordination and optimization of pooled federal resources
- Adopt process mechanisms that embrace a "safe haven" environment for cross-sector, shared dialogue, while ensuring that best practices are fostered
- Assure input and engagement of experts, scientists, and the public, including those who may take advantage of downstream adoption and use VdE innovation
- Encourage development of funding mechanisms, regulatory reforms and federal support systems that are concrete and executable

Adopt a Regulatory Framework to Advance VdE Product Development (in response to questions 5, 13, and 15)

Involvement of the FDA in advancing VdE product development is crucial. One recommendation mentioned in the VdE White Paper, value-driven reimbursement, has recently been adopted:

the pilot program of parallel review by the FDA and CMS. Beyond value-driven reimbursement, the FDA might consider giving priority review of Investigational Device Exemption (IDE) submissions to new products that score high on the VdE value metric. This will not only permit faster clinical trial commencement, but also earlier clinical and design feedback to the product development team. **The FDA can and should adopt its iterative IDE process which, when fully implemented, will permit innovators utilizing VdE principles and processes to start IDE trials early and implement design and protocol iterations based on early clinical results without stopping the initial IDE and restarting**. Within the Premarket Approval (PMA) system, products meeting VdE criteria can be given "fast track" status using internal FDA processes, which does not require legislative action. In addition, the FDA can create internal and external support systems to assist VdE-based products in navigating the regulatory system. Some of these ideas can be incorporated into the recently announced CDRH innovation initiative. CDRH can train and deploy process experts or managers to guide the innovator and the submission through the process; ensure prompt attention to the submission; organize meetings with regulators and the sponsor and generally take accountability and responsibility for prompt review of a VdE-based submission.

RECOMMENDATIONS:

- **Create VdE Scoring metric. Within the Premarket Approval (PMA) system, allow products meeting VdE criteria to be given "fast track" priority status**
- Incent application of VdE principles for the development of medical devices
- Permit the introduction and utilization of computer simulation and modeling as a component in the design and development of VdE devices
- Identify specific medical device testing laboratories with expertise in both physical and computational evaluation of devices coming before the agency for 510(k), IDE, PMA, or humanitarian device approval to provide independent review and validation of a device's adherence to VdE criteria
- Continue to consider market incentives for VdE
- Include enhanced support for the VdE innovator
- Consider VdE principles in reimbursement

Train and Inspire the Next Generation of Engineers (in response to questions 1, 9, and 12)

Value-driven engineers need technical expertise to find feasible solutions to critical problems; however, this is not sufficient. They also need to understand human and societal needs as well as pragmatic aspects of manufacture, context, maintenance, and sustainability to produce solutions that are viable in their intended market or application. Innovation is rarely about technology in isolation.

Educating the next generation of value-driven engineers requires broadening the questions our students are taught to ask. From *Rising Above the Gathering Storm* to *Engineering the Future*, from *Wired to Care* to *Change by Design*, the need for empathetic and entrepreneurial engineers has been widely discussed. The world needs more T-shaped people – with breadth and depth – rather than solely deep – I-shaped – engineers. The challenge is how to educate them.

We learn what we practice. To produce value-driven engineers, we must create educational environments in which our students practice VdE. They must learn to ask their own questions, to set their own problems, to create responsive designs, obtain feedback, build, fail, try again, and persevere; interdisciplinarity and creativity are key. If we want graduates who engineer

value, we must provide our students with opportunities to practice VdE. They must communicate, work in teams, get their hands dirty, self-evaluate, plan, reassess. Only by being apprentice value-driven engineers will they obtain the requisite skills to become masters at this craft.

Fortunately, there are numerous successful examples of educational environments providing exactly this kind of experience, including ABIA; the Center for Bioengineering Innovation and Design program at Johns Hopkins University; the University of Kansas Institute for Advancing Medical Innovation; the Stanford Biodesign Program; the Health Sciences and Technology Program at MIT and Harvard and MIT's Deshpande Center; Olin College; and the NAE Grand Challenge Scholars Programs on many campuses. Identifying other successes and using them as models to share with others represents a first step in educating the next generation of value-driven engineers. It is not, however, sufficient to identify successful models and expect other institutions to emulate them. A long history of failure to widely transplant educational innovation – e.g., the Engineering Coalitions project – serves to underscore the context-sensitivity of education. Ultimately, successful educational innovation is owned by its practitioners and is fitted to the institutional needs and culture in which it thrives. Educational innovation must therefore be co-designed and co-created for its intended context. Thus, our recommendations substantially concern the building of communities (at the post-secondary and K-12 levels, as well as outside of academic institutions).

RECOMMENDATIONS:

- Employ challenge-driven innovation by sponsoring a **VdE Grand Challenge** to encourage innovative and VdE product solutions
- **Develop and offer patient-centered, problem oriented courses** (e.g., biodesign courses at ABIA, Stanford and Johns Hopkins)
- **Encourage entrepreneurship within the university setting** (e.g., ABIA's Women's Entrepreneurship Program)
- Create VdE Training Workshops designed to educate current and future professionals on medical device costs, barriers, streamlining processes, case studies
- National VdE Biannual Conference (April 2012) – gathering of multidisciplinary thought leaders from government, academia, industry, healthcare, venture capital, philanthropy and non-profit sectors, as well as medical device entrepreneurs to foster VdE principles

Conclusion

To sustain U.S. leadership in the $350 billion global medical device industry, an approach that leverages targeted public policy in tandem with private sector efforts is crucial. Deployment of VdE will have significant impact not only on innovation and retaining and creating high-wage, high skill jobs, but also healthcare costs by making the U.S. more competitive in the global market. Although these recommendations have focused on national challenges in health, VdE principles may also be applied to the nation's food, energy, and environment challenges.

References

1. United Nations Educational, Scientific and Cultural Organization and PWC
2. Business Monitor International 2010
3. http://www.abiakron.org/Data/Sites/1/pdf/abiawhitepaper6-14-11.pdf
4. National Defense Authorization Act for Fiscal Year 1996, PUBLIC LAW 104–106—FEB. 10, 1996

Mon 11/21/2011 10:28 PM

RFI-National Bioeconomy Blueprint: San Francisco State U. Professional Science Master's

Dear Office of Science and Technology Policy,

San Francisco State University, located in the epicenter (San Francisco Bay Area) of bio-innovation, has recently successfully instituted an internship-based Professional Science Master's (PSM) program (www.sfsu.edu/~psm; http://www.calstate.edu/psm/) with funding from the Alfred P. Sloan Foundation, National Science Foundation, and the California Institute of Regenerative Medicine. Students in the first PSM cohort admitted in 2010 have completed required bioscience coursework, concluded industry internship training and are applying for or have already entered employment in industry and government sectors. Based on the rapid growth of the STEM workforce and accumulating evidence of training success in similar academic-industry education partnership programs, we urge policy leaders to support interdisciplinary graduate training designed to cultivate an innovative, perseverant and well-trained American workforce to further US competitiveness.

Sincerely,

Lily Chen, Ph.D. Professor

San Francisco State University

Lily Chen, Ph.D. Professor of Biology
Director, Professional Science Master's
in Biotechnology & Stem Cell Science
Principal Investigator- Science Masters Program, National Science Foundation
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Citizens for Responsible Care and Research, Inc. (CIRCARE)
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November 23, 2011

Office of Science and Technology
Policy Executive Office of the President

VIA e-mail: bioeconomy@ostp.gov

In re: Office of Science and Technology Policy, Notice, Request for Information: Building A 21st Century Bioeconomy, 76 Fed. Reg. 62,869 (2011),

These comments respond to regulatory concerns raised in the Office of Science and Technology Policy's Request for Information.

INTRODUCTORY STATEMENT:

We are especially concerned that:

1. Protection of patients and of subjects of biomedical, behavioral, and social research might be perceived as hindering scientific and technical advance; and

2. These protections might therefore be cut back—to the detriment of patients, research subjects, and science itself.

Citizens for Responsible Care and Research, Inc. (CIRCARE) is the oldest human research protection organization in the United States and is entirely independent. We advocate conscionable research. We are private citizens dedicated to effective protection of human subjects in behavioral and biomedical research. Our board members and officers are from science, law, research policy, ethics, medicine, nursing, social work, education, and care-giving. Some of have been voluntary subjects of research. Experience represented in our board and officers includes governmental and academic Institutional Review Board membership and chairmanship and university faculty in national and international law and ethics of human subjects research. We serve without pay. CIRCARE receives no support from industry or government.

The National Bioeconomy Blueprint purposes include "to ... identify

regulatory reforms that will reduce unnecessary burdens on innovators while protecting health and safety ....” Protection of health and safety, including protection of patients and human subjects of behavioral and biomedical research, is not antithetical to nor does it deter well-conceived research. Science and society benefit from a credible, largely earned reputation of medical concern for the public welfare. Medicine, because of its long-established ethical tradition of clinical beneficence and fidelity to the individual patient, brings with it a presumption of trustworthiness.

But as the record shows, there continue to be rogues in research and more than occasional disdain for the dignity and rights of human subjects of biomedical, behavioral, and social research. We continue to encounter disregard for the relevant ethics and law. The most notorious of these violations continue to make it difficult to recruit research subjects even where they stand to benefit. Biotechnology and information technology, including data-mining, are combining to pose serious threats to personal privacy in the course of research, notwithstanding their potential impacts if brought to commercial fruition. Eagerness to minimize human research protections will exacerbate inability to recruit subjects for meritorious studies. Personal medical data essential to validate new medical research techniques and development of diagnostics and therapeutics will not be readily available if researchers cannot be trusted to protect their information from access for which there is no informed consent.

U.S. law on federally supported research and on research in support of Food and Drug Administration indications requires that Institutional Review Boards “review biomedical and behavioral research involving human subjects ... in order to protect the rights of the human subjects of such research,” 42 U.S.C. § 289(a), implemented in the Common Rule, 45 C.F.R. pt. 46, and by the FDA, 21 C.F.R. pts. 50 & 56.

The OSTP RFI rightly refrains from asserting that current regulation to protect research subjects arbitrarily inhibits meritorious research and development. But in a recent Advance Notice of Proposed Rulemaking, Docket HHS-OPHS-2011-0005, 76 Fed. Reg. 44,512 (2011), the Department of Health and Human Services states that existing human research protections constitute undue burden and proposes to foster research by altering dramatically what has been a generally effective, stable, predictable, mostly supportive regulatory environment. We pointed out in response the DHHS ANPRM rests on highly questionable assumptions and its proposed changes would run weaken existing protections substantially, counter to law, and would be to the detriment of science itself. http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2011-0005-0336 and http://www.circare.org/submit/circare_anprm_response_201109.pdf.

We generally endorse the stated “grand challenge” goals:... such as ‘‘smart anti-cancer therapeutics that kill cancer cells and leave their normal neighbors untouched; early detection of dozens of diseases

from a saliva sample; personalized medicine that enables the prescription of the right dose of the right drug for the right person; a universal vaccine for influenza that will protect against all future strains; and regenerative medicine that can end the agonizing wait for an organ transplant.''
Still, as we make plain in our response to the DHHS ANPRM and in our comments above, we must be very careful to ensure protection of health, safety, and the rights and dignity of patients and research subjects and that the "burdens" reduced are in fact "unnecessary." We note that reaction to the DHHS ANPRM has been mixed, with some research institutions finding the proposals impractical, and we see with dismay that many of the comments that favor the proposed changes seek only convenience and freedom from regulation.

Some of the responses to the DHHS ANPRM, especially from behavioral and social science, contend that protection of human subjects of research restricts academic freedom. These are not separable concerns, in view of increasing interest in conjoining behavioral, genetic, and neural science and technology. We remind you of the legal and ethical adage that one's freedom to swing a fist ordinarily ends where another's nose begins.

CIRCARE RESPONSE TO QUESTIONS IN OSTP RFI:

"(13) What specific regulations are unnecessarily slowing or preventing "bioinnovation?"

"Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment."

We commend OSTP for insistence that evidence of regulations' having slowed "bioinnovation" be specific. Although the human subjects regulations have been termed complex and overprotective and an unnecessary "regulatory barrier" or "regulatory burden," we have seen no evidence to support those assertions. To the contrary, we see a continuing need for effective regulation to protect research subjects and patients. See Howard Brody, *The Future of Bioethics* (Oxford University Press 2009).

The project launch delays that we have seen in human subjects research were attributable largely to institutional procedures unrelated to regulatory responsibilities; to Institutional Review Board concerns that sponsor demands were insufficiently protective; and to investigator failure to meet even minimal requirements for human subjects protection.

Where we have seen delays in mounting multi-site studies, the delays have been attributable to failure of one or more IRB's to spot a critical ethical problem.

On the other hand, we have seen the necessity for pulling back newly developed FDA-regulated articles because information material to FDA decision

and patient protection had been withheld. We have seen delays in marketing of needed FDA-regulated articles because of laxity in manufacturing practices and failure to assure safety and quality of chemical feedstocks.

Delay attributable to protection of human subjects will be minimized by strengthening the legal and technical direct-hire staffing of the DHHS Office for Human Research Protections and FDA; by fostering agency willingness and capacity to issue clear regulatory guidance, to audit, and to enforce; and by making the regulatory environment more stable, predictable, and effective.

Centralizing the IRB system, as some critics urge, would destroy a relatively simple system of audited institutional self-regulation, it would minimize the role of local knowledge in ascertaining vulnerability of individuals who might be research subjects, and it would lead to a tremendously complex system of voluminous, time-consuming information exchange for which there are no foreseeable federal resources.

(14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

Department of Health and Human Services:

> Retain the Common Rule and its FDA implementation without amendment, and use agency notice-and-comment guidance to deal with questions of interpretation. Changing the system would render the current, easily understood system less stable and less predictable and thereby lead to unnecessary delay, perhaps exacerbated if the Congressional Review Act comes into play.

Food and Drug Administration and
Office for Human Research Protections:

> Minimize inconsistency and increase quality and predictability of IRB outcomes and credibility and trustworthiness of IRB processes and human subject protections by requiring that IRB decisions be reasoned decisions on the record, redacted only for trade secrets, and that they be timely published—electronically and searchable.
>
> Audit the provenance of biospecimens in OHRP-overseen research, in order to ensure that (a) these materials have been obtained in compliance with the letter and spirit of human subjects protection requirements, (b) associated genomic and other donor data are credible, and (c) these materials have not moved through a black market in human tissues.

Food and Drug Administration,

Office for Human Research Protections, and
National Institutes of Health:

In order to enhance subject protection, cut unnecessary delays in worthy product development, and cut the time spent on activities apparently leading to failure: Clarify the duties of data and safety monitoring entities to emphasize that subject safety is the paramount consideration, and require these entities to report their basic reasons, not merely there conclusions, in their recommendations to stop or suspend trials or to continue trials as open-label and cross-over.

Office for Human Research Protections:

Education and training:

Reorient internal and external training programs and materials to recognize that the Common Rule itself recognizes that it is not the only applicable law and that IRB's must take into account all relevant law. The current focus is misleading and narrow, dealing almost exclusively with the Common Rule.

Reorient internal and external training programs toward the goal of legislative and regulatory intent, expressed in the Belmont Report and in statute, of protection of the rights of research subjects. The current focus is misleadingly on compliance minima irrespective of project and research population.

Train institutional officials and trustees on obligations under assurances.

Enforcement:

Strengthen OHRP direct-hire enforcement capacity, especially with qualified legal talent, to improve the agency's regulatory credibility, consistency, and predictability.

Audit compliance with U.S. and foreign institutional assurances, to improve the agency's regulatory credibility consistency, and predictability. Use direct-hire staff for this purpose.

Timely web-publish warning and enforcement actions, for easy searching, so as to foster compliance and predictability in the system.

Take seriously the applicability of international law, under which

> the United States also has obligations for its activities at home and abroad, and foreign law where U.S. researchers and research entities are involved. OHRP's website publishes a useful, if inevitably incomplete and non-authoritative, compilation in this regard. But OHRP, research institutions, and even many in the research bioethics community seem not to accord that law any significance.

Office of Information and Regulatory Affairs, and
Office of Science and Technology Policy:

> Ensure that regulatory development and interagency proceedings, including harmonization of agency guidance to the extent practicable and desireable for human subjects protection be public and on the record, with all ex parte contacts made public also in a timely and readily accessible way.

(15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

Office of Science and Technology Policy:

> Biomedical research and development and the biotechnology, biomedical, pharmaceutical, and research instrument industries are transnational. Whether here or abroad, medical development can be hindered or fostered by patent law and practice. Privacy law differs substantially, relevant European law being more protective generally than that of the United States. Law and practice regarding product safety differ substantially from country to country. We urge that as these issues are reviewed the rights of patients and research subjects and the safety of products and practices be considered paramount.

Responders are free to address any or all the above items, as well as provide additional information that they think is relevant to the development of a National Bioeconomy Blueprint.

As we state above, OHRP and FDA both need strengthened direct-hire legal and technical resources for enforcement (OHRP as to whether human subjects protection requirements are met for federally supported research, andFDA as to whether a broader array of requirements are met for research in support of applications for indications).

We will be pleased to be of further assistance.

Sincerely,

For Citizens for Responsible Care and Research:

Gerald S. Schatz, J.D.

(Of the Bars of the District of Columbia and Pennsylvania)
Vice President, CIRCARE

Reply to: Elizabeth Woeckner, M.A.
President, CIRCARE
[redacted]

Or:

Gerald S. Schatz, J.D.
Vice President, CIRCARE
[redacted]

Subject: Community colleges and the bioeconomy
Sent: Fri 11/25/2011 5:12 PM

This email is in response to the question in the RFI on the role of community colleges in training the bioscience workforce.

Community colleges play a critical role in this endeavor for a number of reasons.

1. Community colleges are a major provider for the kind of training and skills that students need in the bioscience industry. This need is not met adequately by four year schools and universities.

How do we know this?

We hear this from our industry advisory board members. They request that we include specific skills in our curriculum and knowledge about industry practices, such as the need to follow FDA guidelines such as GMPs, GLPs, and GCPs. They also want us to make sure students know how to keep industry quality laboratory notebooks and make sure student have lots of hands on practice with skills in metrology. All students need to know how to make buffers, media, and other solutions; adjust and measure pH, and calibrate equipment.

Evidence: Every year I get several students in my bioinformatics class who already have a four year degree. During the past two years, 54 out of the 84 students in the bioinformatics course that I teach at Austin (TX) and Shoreline Community Colleges (WA) have stated that they have bachelors degrees in either biology, chemistry, or a related field. They take my class because they wish to learn how to use bioinformatics applications in biotechnology.

2. Professionals who work in the bioscience industry have ongoing needs for retraining and new training. The bioscience industry needs these activities in order to survive. Community colleges, with their ability to hire part-time instructors from industry, are uniquely positioned for quickly starting new classes to train students in new technologies.

In Washington state, biotech companies have short (5-10 years) life cycles. They start, they hire new technicians, they develop a promising technology, they get purchased by a larger company, then several people get laid off.

This means that every five years, people are back in the job market and looking for ways to learn new skills and upgrade existing skills. Community colleges meet an important need in this area by giving people the chance to learn new skills without investing years in getting a new degree.

It's important from the standpoint of companies that they be able to hire people with the specific skills for the job. At the same time, small companies can't promise to give people jobs for life. Companies are only able to work on new technologies if workers have the ability to exit and reenter the labor pool,

Many of my students have been in situations where they've been working at biotech companies, but the companies have been subsumed and they need to move on.

Some students also change careers. One of the PhD scientists who took my course went on to become a patent lawyer.

How can community colleges continue this work?

It is important for organizations like the National Science Foundation to continue funding innovative programs at community colleges. I have been part of an organization, Bio-Link, that has received funding from the NSF. Through Bio-Link, we have built a national network that allows innovative practices to be shared and spread from one college to another. If it weren't for the Advanced Technology Education program at the NSF, the innovative ideas would never have gotten the opportunity to be tried, let alone spread to other colleges.

Sandra Porter, Ph.D.
www.bio-link.org

Office of Research
Center of Excellence for Regenerative Health Biotechnology

13706 Innovation Drive
Alachua, FL 32615
[redacted]

November 28, 2011

The White House
Office of Science and Technology Policy
bioeconomy@ostp.gov

Re: **Request for Information: Building a 21st Century Bioeconomy**

Dear Sirs,

I strongly support President Obama's initiative to develop a National Bioeconomy Blueprint.

The University of Florida's Center of Excellence for Regenerative Health Biotechnology (UF CERHB, http://cerhb.ufl.edu/) is a biomedical translational research support center with the mission to stimulate promising research and facilitate first-in-man studies, leading to commercialization of technologies that will provide treatments for human diseases, as well as create new companies and high-wage jobs.

We are positioned at the interface between industry and academia to provide expertise, training programs, and drug manufacturing services to the biotechnology industry and to biomedical research institutions.

Established with state and federal funding (US Dept. of Commerce EDA), our 23,500ft^2 cGMP biopharmaceutical development operation (Florida Biologix®, http://www.floridabiologix.ufl.com) offers a wide range of affordable biopharmaceutical manufacturing and testing services. We have manufactured over 50 product lots since 2007, including cell and gene therapies and proteins expressed in mammalian cells, and provide aseptic filling, product testing, and regulatory support. Products made in our facility are suitable for Phase I and II human clinical trials, offsetting common barriers of bringing laboratory discoveries to the clinic, such as the high operating cost of cGMP compliant manufacturing and regulatory expertise. Client sponsors include Florida companies, start-up companies, multi-national and foreign companies, domestic private and public companies, academic scientists, and the NIH.

The UF CERHB Education and Training Center (http://cerhb.ufl.edu/education_index.html) was established as a biotechnology education resource to prepare a technical and knowledge-based workforce to support the growth of the biotechnology industry. We have brought together elements needed for a fully integrated biotechnology education program. Developed with deep industry involvement, our curricula are focused on fundamental science applied to biotechnology product development, manufacturing process development, analytical technology development, regulatory compliance, and commercialization. Hands-on STEM-based curricula with a focus on Industrial Biotechnology were developed at the college and high School levels (funded by NSF).

In anticipation of these new course offerings, the UF CERHB submitted a 3-year curriculum in industrial biotechnology to the Florida Department of Education, which approved the coursework for both academic and Career and Technical Education (CTE) credit in December, 2006. Offered for the first time in the Fall of 2007, the program now spans the state with over 900 students currently enrolled. Teacher training programs were also developed by the UF CERHB to provide district certification for teaching the CTE component of the secondary program, and to assist teachers in the preparation of teaching science and its tools, as a means of discovering, developing, and testing products for use in humans and commercial sale. An industry-recognized credentialing exam was created and is administered by the UF CERHB (funded by US DOE OVAE/Florida DOE), as a mechanism for graduates of the secondary program to demonstrate mastery of bio-industry based skills and knowledge for employment, or for statewide articulation into post-secondary A.S. degree biotechnology programs. We have found that framing basic science concepts in the context of their application to product development and careers in the biotechnology industry engages the students at a level that motivates them to succeed.

To address immediate and emerging workforce needs, hands-on curricula in Industrial Biotechnology were developed (funded in-part by WorkForce Florida, Inc.) for entry-level and incumbent workers. Additional courses continue to be developed as the industry grows and matures in Florida. An Advisory Council has been assembled comprised of leaders from industry, workforce boards, and economic development agencies from across the state. Industry focus groups, a needs assessment, and surveys have been conducted to determine the needs of Florida companies. Based on this input, highly relevant short courses that combine classroom and wet lab training have been developed, each of which leads to an industry-recognized certificate. These courses were rolled out in 2007, and we now have over 300 graduates. Furthermore, a novel Masters Program titled “Science Master’s Program in Translational Biotechnology” was established in 2010 (funded by NSF). It is a two-year program that is interdisciplinary (biosciences and business), is research intensive, has industry involvement, and includes a formal internship at a company. Students will graduate with a major (Master of Science in Medical Sciences) and a minor in business administration (Graduate Business Minor), well prepared for immediate employment in mid-level industry positions

UF CERHB has established an extensive support and participation network including companies, research institutes, professional societies, industry organizations, chambers of commerce, materials and equipment suppliers, business development boards, community colleges, school districts, regional workforce boards, and international research collaborators. These partners are motivated to work with UF CERHB to implement the programs and services statewide, nationally, and internationally. I feel that we have built high quality programs that can be replicated throughout our country, and may serve President Obama’s initiative well.

Establishing active private-public partnerships that support and accelerate innovation to move biological research discoveries from the laboratory to the clinic and market is critical. The three suggestions below are made in this context:

1) Establish private-public resources at the local, state, and federal levels using the successful UF CERHB model as a template.

2) Establish public-private partnerships that can facilitate first-in-man studies by establishing programs to support the manufacture and testing of novel candidates, before venture funding is made available. More funding is needed to ensure that technologies can reach their full potential, but rigorous evaluation of the technology, its market potential, competing technologies, business model, and medical need should be conducted as a condition for funding, and this can be ensured/administered by a center such as ours.
3) Provide additional funding for programs that better prepare scientists and engineers for private-sector bioeconomy jobs, beginning in high school and at all post-secondary levels. The majority of Ph.D., MS, BS, AS, and high school graduates will accept jobs outside of academia, yet very few students are exposed to the job and career profiles available to them in the life sciences industry. The education and training these students receive in the basic sciences can be applied and focused to enable them to succeed in industry. Furthermore, with an understanding of drug development, regulatory compliance, quality systems, and manufacturing technologies, these students are more attractive to companies for hiring. Companies benefit too since, once hired, these students can contribute productively to a company in a shorter timeframe, and with less mistakes.

The active leadership by a University in working with high schools, community colleges, workforce boards, economic development agencies, and the industry sector has proven effective. The cornerstone of transferring discoveries to the marketplace is the merging of academic scholarship and research with an understanding of the regulatory processes as they apply to product development, manufacturing, and clinical testing. Designed to facilitate industry growth, our models for affordable biopharmaceutical manufacturing and testing services, and statewide opportunities for workforce and professional training support the state's initiative to promote commercialization and are integral pieces in the infrastructure for building a domestic bioeconomy that is competitive globally.

I would be happy to discuss these ideas further and invite you to visit UF CERHB.

Sincerely,

Richard Snyder (electronic signature)

Richard O. Snyder, Ph.D.
Director

cc: Dr. Winfred M. Phillips
Senior Vice President for Operations
Chief Operating Officer
University of Florida

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November 30, 2011

Dear Mr. President,

On behalf of Research!America, the nation's largest not for profit alliance working to make research to improve health a higher national priority, we are submitting recommendations in regard to your *Building a 21st Century Bioeconomy* initiative.

Research!America fully recognizes that, as stated in the Office of Science and Technology Policy's Request for Information (RFI), our nation is confronting "lean budget times." Our growing deficit is a threat to our country's future prosperity and the viability of the bioeconomy sector. We believe that reducing support for health and medical research at this critical time will not work to reduce the deficit; in fact, just the opposite would occur. Diminished investment in health and medical research would come at the expense of economic growth and runaway federal health care spending. That is why it is critical to include robust investment in such research as a key component of your Bioeconomy Initiative.

Innovation is the catalyst for economic growth, and health and medical research has proven itself again and again as an economic force in this country. A recent report by United for Medical Research found that in 2010, National Institutes of Health (NIH) funding generated more than 484,500 jobs and produced $69 billion in economic activity[i]. A report on the human genome project, prepared by the Batelle Technology Parnership Practice, reported that the initial government investment of $3.8 billion has so far generated revenues of $796 billion dollars.[ii]

In terms of deficit reduction, the nation cannot afford to ignore the ballooning costs of conditions like Alzheimer's, diabetes and obesity. Research supported by the NIH, CDC, NSF and AHRQ are essential to stem the massive increase in Medicare, Medicaid and VA spending that will occur in the absence of effective treatments.

Chronic diseases now account for over 75 percent of healthcare costs and are the main cause of the fast rising burden of healthcare throughout the world. Finding innovative solutions to reduce this burden will not only be the right thing for America to do but one of the most effective way to

overcome the threatening impact of uncontrolled healthcare costs on our economic competitiveness.

Despite great scientific advances, our understanding of chronic diseases is still insufficient to be translated into revolutionary therapies. A bioeconomy for the 21st Century will require continued research investments despite budgetary constraints, as research offers the best hope to curtail the enormous costs bearing down on our nation.

Basic science supported by the National Institutes of Health and other health agencies at universities, academic medical centers and independent research institutions across the country lays the essential groundwork for biomedical products. If we neglect basic research, innovation will slow and the bioeconomy will not meet its full potential. Support for basic research sews the seeds for new business development, new products, and new jobs.

In addition to urging you to include robust funding for health and medical research as a key component of your Bioeconomy Initiative, we offer the following additional recommendations:

Support for the National Center for Advancing Translational Science (NCATS)

In recent years, basic researchers have made tremendous progress in identifying the molecular causes of disease – discoveries that have led to hundreds of potential new therapeutic targets. The rate at which these discoveries are moving from lab to the clinic has been very slow, however. It is estimated that therapies exist for just 200 of the more than 4,000 conditions with known molecular causes. The bottlenecks that exist in our translational pipeline slow the process, add expense and cause the American public to ask, with increasing urgency, why we are not making more progress with medical research. Research!America strongly supports the creation of the National Center for Advancing Translational Sciences (NCATS) at the NIH.

A strategic driving force of NCATS will be to generate innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics. An important goal is to significantly reduce what currently takes about 15 years from molecular discovery to new therapy. Fulfilling the mission of NCATS will require participation and partnership from academia, industry, patient advocacy groups, regulatory agencies and philanthropies in order to drive forward the science of translational medicine. NCAT's activities will complement, and not compete with, translational research being carried out in the private and public sectors today.

Advancing Regulatory Science Initiative (ARS)

Research!America commends the Administration for building on such programs as the Critical Path Initiative to explore how to improve the regulatory environment at the Food and Drug Administration (FDA). Whether it is developing viable models for assessing risks versus benefits or establishing new biomarkers to keep pace with rapidly evolving bioscience, better equipping FDA to fulfill its critical role can help speed safe and effective treatments to the market, bolstering the bioeconomy. Underfunding FDA is a surefire strategy for erasing

any progress made by improved regulatory science. Sufficient resources are a necessity if FDA is to assess new products on a timely basis.

Global Health Research and Development

Throughout the United States, investment in global health creates jobs and drives the economy. For example, Product Development Partnerships (PDPs), non-profit organizations that harness business, government, the philanthropic sector and the academic community to research and develop new life-saving health care technologies for the world's neglected diseases, are supplying jobs and revenue in the United States. The New Jersey based company, Temptime Corporation, partnered with the product development partnership PATH and USAID to develop color changing stickers to determine if vaccines are still effective after shipment. These stickers are used around the world. Importantly, they are now being used locally; for example, in 2009 H1N1 vaccines all came with the Temptime stickers. Global health R&D funding also led to a Chicago researcher's discovery of today's primary treatment for bladder cancer—the tuberculosis vaccine BCG. These are just two of many illustrations of how investing in research to boost the bioeconomy bears fruit, whether that research is focused on domestic or global issues.

Thank you, Mr. President, for promoting the bioeconomy as critical to our nation's prosperity now and in the future, and for considering our view that robust funding for medical research is a sound strategy for furthering your goals. We stand ready to assist you and the OSTP in further shaping and executing your time-sensitive initiative.

Sincerely,

Mary Woolley
President

---

[i] United for Medical Research Report. "An Economic Engine." Published Fall 2011

[ii] Battelle Technology Partnership Practice. "Economic Impact of the Human Genome Project." Prepared May 2011

SBIR/STTR - Revisions Needed to Improve Productivity and Competitiveness
Wed 11/30/2011 8:33 PM

Dear Persons,

Thank you for giving us the opportunity to provide suggestions to enhance and improve the Bioeconomy in the United States.

While Cognosci and myself much appreciate the SBIR/STTR program, part of the NIH specific rules now state that a grant proposal may be submitted followed by one (and only one) revised proposal.

We believe this policy to be regressive and unfair and should be changed.

For example, we propose that as long as a grant application is scored, one should be permitted to revise the proposal (according to the helpful suggestions from the reviewer's on Study Section) and re-submit the proposal for additional review and potential funding. Such an approach would not end promising projects before they had a chance to be properly heard and matured.

In addition, we strongly suggest that Study Sections (organized by the Office of Scientific Review of the Extramural part of NIH), especially those that deal with commercializable matter as seen in SBIR/STTR applications, should be composed of at least 75% of scientists with industry experience. The current constitutions of most SBIR/STTR sections is far less than 50% of persons that come from industrial/pharmaceutical/biotechnology backgrounds. Thus, the criticisms of the SBIR/STTR grant proposals are inappropriately weighted to more professorial/academic concerns, that largely are not part of the commercialization process.

These changes would not cost any taxpayer 1-dime over the current costs of these SBIR/STTR programs. They would, however, improve the likelihood that commercially viable projects in biotechnology fields would have a chance to be funded, to be developed and commercialized, while employing highly skilled scientists and professionals.

Thanks for your time, and we would be happy to answer any questions on this topic if you would like further input.

Thanks,

Mike Vitek

Michael P. Vitek, Ph.D.
Chief Executive Officer
Cognosci, Inc.

Wed 11/30/2011 8:43 PM
SBIR/STTR - Proposal to change set-aside amounts for funding

Dear Persons,

The SBIR/STTR program is in danger of loosing its pre-eminent status as a supporter and developer for innovative technologies and products for the health, agricultural and energy sectors.

I would strongly urge the committee, the President and Congress to increase the set-asides that are part of the existing budgets to NIH, DOD and other agencies from 2.5% to 3.5% or even 5% of those budgets.

For example, in the case of NIH, the majority of translational activities where research at the bench leads to compounds that are developed in clinical trials and then sold on the market are coming from small companies. While intramural NIH continues to attempt to develop drugs, and so do many academic medical centers, the real drive and ability to develop drugs comes from companies, particularly small business. While the ownership of patents may be great for academic non-profit institutions, those patented discoveries often languish in the institutional portfolio and are largely lost to help patients with diseases.

Research on not-for-profit institutional patented materials, if they are to developed into drugs that improve the public health, should be increased to accomplish the likelihood that the public health will be improved.

Thanks,

Mike Vitek

Michael P. Vitek, Ph.D.
Chief Executive Officer
Cognosci, Inc.

1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

Reply to 1)

The best grand challenge that I can think of is 4) which you have listed below – a dedicated effort to determine the function of genes. Please see my reply to 4).

Research and development: R&D investments, particularly in platform technologies, can support advances in health, energy, the environment, and agriculture, and accelerate the pace of discovery in fundamental life sciences research.

2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

Reply to 2)

This is not really an issue of constrained budgets. Federal funding should always look to fund high-impact research and innovation. However, innovation often comes from small projects. The research budget is better spent when it also reserves sufficient funding for more researchers to seed many projects. In the past decade, there is a trend to fund larger research proposals often with multiple investigators. Overall, it is better to fund more single investigator projects, which are more carefully conceived and where the responsibility for success lies directly on that investigator.

3) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative[1])?

4) The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

Reply to 4)

Yes, you are exactly correct in identifying this issue as a key bottleneck in biology R&D. In fact, two core technologies already exist for tackling the problem. So the hurdle here is not that we need to invent new technology. We mostly need to fund projects to utilize the technology that we have. In doing so, the developers and sellers of the technology, such as

our company Biolog, Inc., will be able to reduce the cost and improve the technology, just as the cost of DNA sequencing has plummeted as the speed and accuracy has improved after the government provided funding for large scale sequencing projects. Prioritizing and funding an appropriate number of large scale and high profile gene function projects (for example within Core Facilities) will also have the beneficial effect of making these technologies available to more labs at lower cost.

One technology that I am referring to is high throughput (HTP) image processing. Gene engineering technology allows construction of cells with green fluorescent protein (GFP) fused to protein-coding genes of interest. HTP image processing can then be used to determine if and where the protein localizes within the cell. The location of the protein provides insight into and validation of the protein function.

The second HTP technology, which was developed by our company more than 10 years ago with SBIR funding, is Phenotype MicroArray (PM) technology. This technology employs a redox dye to precisely measure cell energy production in thousands of microwells, with each well measuring the activity of a different cell pathway or phenotype. With this technology one can directly compare two cells, one with a knockout or other alteration of a gene of interest. It provides a direct assay for gene function as it measures the biologic consequences to the cell of altering a specific gene. The technology can be used with bacterial, fungal, and even human cells and has already been proven to work in hundreds of scientific publications. It can be termed a metabolic and physiologic or a chemical biology approach to determination of gene function and it is quite different from and complementary to the image processing technology.

The potential benefits of funding the adoption and use of these pre-existing technologies are enormous, ranging from treatment of disease and drug discovery to improving the engineering of microorganisms for more efficient energy and biofuel production by microorganisms. I would be happy to provide much more detail in support of these contentions described above.

Moving life sciences breakthroughs from lab to market: It is a challenge to commercialize advances in the life sciences because of the risk, expense, and need for many years of sustained investment. The Administration is interested in steps that it can take directly, but is also interested in encouraging experimentation with new private-sector-led models for funding commercialization of life sciences research.

5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

Reply to 5)

Our company has encountered regulatory barriers from the FDA. See my Reply to 13) and 14) below. If our product had been cleared years ago, we would have a lot more sales and would have substantially increased our hiring.

6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs [2] would help accelerate commercialization of federally-funded bioeconomy-related research?

Reply to 6)

I and my company Biolog Inc., have benefited greatly for more than 20 years from the SBIR Program. It is very well run and very well administered. The main problem that I have noticed more and more each year is the deterioration of the quality of scientific reviews of SBIR proposals. The reasons for this are clear. They cannot recruit top scientists for these panels because they are already over-committed. It is a lot of work to serve on these review panels and it is somewhat of a thankless job. There has been and continues to be a deterioration of the quality of scientists serving on these panels and/or the time and thought that these scientists are able to donate in reviewing proposals. I have three suggestions on this. One is to use older and retired scientists with greater knowledge and broader experience in these review panels. Another is to pay scientists for their time spent in reviewing proposals. A third idea is to have a system for grant submitters to rate the quality and accuracy of the reviews that they receive so that unskilled and unqualified reviewers get filtered out of the review process.

7) What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

8) What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

Reply to 8)

See reply to 13 below.

Workforce development: Investment in education and training is essential to creating a technically-skilled 21st century American bioeconomy workforce.

9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Reply to 9)

Our biotech company has no problem finding skilled scientists that want to do experimental work, but we have great difficulty finding skilled scientists that want to work in sales, marketing,

and manufacturing. Programs should be established or modified to train or retrain scientists to work in these alternative but equally-important areas.

10) What roles should community colleges play in training the bioeconomy workforce of the future?

11) What role should the private sector play in training future bioeconomy scientists and engineers?

12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

Reducing regulatory barriers to the bioeconomy: As President Obama has stated, our regulatory system must "identify and use the best, most innovative, and least burdensome tools for achieving regulatory ends" and "protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation."

13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

Reply to 13)

The government should update the laws to make it easier for small companies to go public - in particular they should change investment banking regulations and Sarbannes/Oxley.

The USA has been the envy of the world for innovation and startup high tech companies. We are rapidly losing that enormous advantage. Because of Enron and other misguided businesses, which had nothing to do with high technology, the Congress over-reacted as it often does, and changed the laws making it much more expensive and difficult for companies to go public and gain access to crucial public funding. They essentially threw out the baby with the bath water.

What really needed to be reformed was the investment banking field, their conflicts of interest, and their stranglehold as gate keepers of public money. The internet is a great thing, but the internet bubble demonstrates the unreliability and greed of much of the investment banking community.

Currently there are 2 major sources of capital for developing high technology and products: (1) venture capital, and (2) government funding, especially the SBIR Program. Venture capital works for certain situations. In our case our company received most of its money from SBIR. We have been a profitable company for most of our 25 years in business, we employ about 40 people, mostly in California, and we sell 60% outside of the USA. We have an innovative and totally unique biotechnology product portfolio and our products support many other companies in developing and producing better products of their own.

However, our business is still relatively small. I would like to expand our business, but it would mean taking private investment which always comes with many strings attached. Private investors demand preferred stock which means that if the company stumbles, the current owners can lose their entire share. These private investors will also usually demand faster return on their investment and, in doing so, force small companies to sacrifice longer term stability and growth for earlier, shorter term returns. Therefore we chose to not take private investment money and to grow slowly, as our limited capital resources permit. What we would really like to do is to go public, raise public capital, and grow the business in partnership with our public investors. However there are two major hurdles: (1) investment bankers demand a heavy toll, and (2) Sarbannes/Oxley makes it very expensive for a smaller company to comply. The company Google showed a better approach to going public, using a public Dutch auction instead of buckling under to investment bankers. This should be a model to replace the current stranglehold of investment bankers. Set up a process for complete public disclosure and make it simple and inexpensive for companies to go public via a supervised internet auction.

As CEO and CSO for Biolog I try my best to always look at the future and serve as company visionary. High tech companies often need to be led by visionaries. Steve Jobs showed that very clearly in his start-up and his turnaround of Apple. Simply stated, smart government policy would encourage visionaries by keeping down the barriers to starting new companies and the barriers that prevent them from gaining access to public funding.

14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

Reply to 14)

In our case, we have had issues with the FDA in trying to get our bacterial identification products approved for sale to clinical laboratories. We feel that the rules that the FDA has established are too vague, too arbitrary, and have been applied more stringently against our company (a small US company) compared to our two main competitors (a large French and a large German company). I would be more than happy to discuss the details privately.

15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

Reply to 15)

The FDA, the drug companies, and the overall drug approval and drug liability process are a huge problem that needs a massive reform.

Let me start with the drug companies. They are both the cause of problems and also victims. To promote innovation, the largest pharma companies should be broken up. The US government made a huge mistake by allowing so many mergers. The industry was much

healthier and much more productive when there were 30 pharma companies instead of 5. When the companies are smaller there is a much greater diversity of ideas and research projects. There is also greater competition. When the companies are too large, they have to find drugs with multi-billion dollar potential, so they focus in a few areas and ignore important diseases that are not as common. They also become very fearful of making mistakes and getting sued.

The FDA has no incentive to streamline the approval process. Hospitals and clinical trials have become much too slow and expensive. This kills innovation and slows the discovery and release of important new drugs.

Lawyers are an enormous and unproductive leach on the entire process. If a drug clears all of the FDA hurdles and reviews, it should be immune from law suits. Pharma companies should be relieved of this huge non-productive burden. Instead, more money should be spent to monitor for problems after the drug is on the market. This is a good and valid use of money. If a drug proves safety and efficacy to the current state of science, but later turns out to have an unforeseen detrimental effect, then its use for certain patients should be curtailed or it should be taken off the market. Pharma companies should not be shaken down by law suits. When people chose to take new drugs, they are clearly taking some risk. Life has risks and people must make choices. When lawyers and injured parties win in the current law suits, many other people lose because the money is not used in the development of newer and better drugs and devices.

FDA regulation of diagnostics should also be reformed. See my Reply to 14). In this case, I think that regulations defining what is needed to market a device for identification of bacteria in hospitals should be determined not by FDA staff but by an independent qualified committee of scientists with detailed knowledge of this field. The committee should meet every year to decide if and how the regulations should be modified. The same should be done with regulations defining what is needed to market a device of determining antibiotic susceptibility. The current regulations are inappropriate, unnecessarily expensive, and stifle innovation.

Public-private partnerships: The Administration is interested in serving as a catalyst for public-private partnerships that build the bioeconomy and address important unmet needs in areas such as health, energy, agriculture, and environment.

16) What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

17) What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

Request for Information: Building a 21st Century Bioeconomy

This response to the RFI posted in the Federal Register Vol. 76, no. 196, Tuesday Oct 11, 2011 will focus on three areas: moving life science breakthroughs from lab to market, workforce development and public-private partnerships.

The views and suggested approaches expressed below represent my own personal views and do not necessarily represent the views held by the Partners Healthcare organization. I am submitting this document as a private citizen.

Moving life science breakthroughs from lab to market:

There are a number of challenges affecting the translation of biological discoveries into products. These start at the level of the investigators who traditionally have no training in development, nor really any interest in doing this type of work. This is not surprising as not only do they not have this training, they are also not rewarded in their career development for performing translational research that may or may not lead to publications or research grants. Thus, institutional policies for promotion need to recognize this effort as important and as a criterion for career advancement in order to begin to change this culture. Funding for these types of activities is also a challenge. Historically, institutions looked to private sector funding to support these activities. While some federal funding has been available through specific programs such as the SBIR/STTR programs and now potentially through specific initiatives catalyzed by the NIH's National Center for Advancing Translational Sciences (NCATS), federal funding , at least in the life sciences, has been devoted primarily to funding hypothesis-driven research. In addition, mechanisms for review and granting of federal funds tend to have a very long timeline and tend to focus on strength of science rather than commercial potential. Further, funding from the private sector including companies and private investors has been markedly reduced since 2008 given the inherent risks and uncertainties in the commercialization of discoveries from the life science sector. Concerns around conflict of interest or perceptions of conflict still surround academic and government institutions, particularly when investigators continue to be involved in technology development through a startup venture or other mechanism that creates a potential financial incentive for the investigator.

Suggested approaches:

1. Changing the academic/governmental institutional culture regarding translational research/R&D: Firstly, this type of activity must be recognized as important to the institution as demonstrated by vocal support from senior administrative officials. This could go as far as incorporating some aspect of the activity (translational research, innovation advancement) into the mission statement of the institution. Secondly, promotion criteria must reflect and take this type of activity, as well as activities which support innovation, into account. For example, promotion criteria could include patents issued, technology licensed, products developed as well as accounting for time spent in these and mentoring activities, such as advising less experienced investigator/entrepreneurs. Lastly, it is not enough to partner basic scientists with clinicians and expect that the result will be translational research/technology advancement. In industry, technology development is a rigorous process based on achieving well defined milestones responsive to market needs. Academic scientists do not work this way, however, it is possible to partner academic/clinical researchers with scientists/engineers trained in this

process (usually coming from industry) to capture the best of both worlds – cutting edge research and technology advancement (see section on Public-private partnerships).

2. Funding: In this current economic climate, there is no question that funding is an issue. Industry, particularly the pharmaceutical industry, is looking at significant losses in revenue and meager pipelines. At the same time, many companies have down-sized by laying off R&D personnel, further compromising the ability to replenish pipelines. Academic institutions need to play a larger role in advancing technologies in the life sciences/healthcare sector to help feed pipelines and decrease technology risk. The question is how to fund these activities, as the traditional private sources (companies, venture capital) have dried up and non-profit (federal sources) have not historically supported this type of work.

   One exception is the SBIR/STTR programs which have played a role in supporting the activity. Both programs are set up to require industrial collaboration with a small company that is not institutionally controlled. This requirement is often met by setting up a shell company – which was not the intent of the provision to begin with – the intent being the demonstration of market/industry interest and economic impact. In addition, the creation of a startup company to advance technology can create downstream conflict of interest complications with respect to investigator financial interests. One possible modification of the SBIR/STTR program is to allow funding to come directly to the institution providing that the institution can create a compelling business case and demonstrate market need and/or interest. This would allow advancement of different types of technologies, not just platform technologies that could support a startup, but also improvements which could be licensed to existing companies to supplement their business interests.

   The SBIR/STTR program would be much more effective if the timeline for seed/phase 1 grants could be shortened. In this day and age, technology development moves at a fast pace – in fact all research has essentially "speeded up" given access to automation and new platform technologies. The NIH granting process, has not however, kept up with this pace. This problem is more acute in the translational area as funding from the private sector is typically contingent upon the successful conduct of key proof of principle experiments (funded by SBIR/STTR programs). The hiatus between grant submission and release of funds can result in loss of private funding and/or loss of key personnel.

   Funding directed to translational research or technology development could also facilitate access to company technologies and expertise that could be used to understand pathways/targets so as to develop more effective therapies. There is a significant amount of knowhow and expertise in pharmaceutical, device and diagnostics companies that is currently not shared. Companies have approached academia with a willingness to share information and work together to develop new therapeutics, diagnostics and devices. However, in many cases, the only resource the company can offer is expertise/knowhow. Funding is extremely tight and without funding, the academics and clinicians are not able to work in partnership to conduct this important research. A mechanism by which federal funding could be accessed through an expanded SBIR/STTR mechanism or other mechanism could serve to catalyze these types of partnerships.

3. Conflict of Interest: While this is a serious matter affecting public trust, our current climate is very strict with respect to involvement of entrepreneur/investigators in the downstream

advancement of their technology. Our current guidelines/policies essentially prohibit any involvement of the investigator in clinical research if the investigator has a financial interest in the technology. Thus for an investigator to remain involved in development of his/her technology, s/he must eschew any financial interest which includes stock/stock options (in startup companies), cash payments above a de minimus level –and now there is discussion regarding royalty payments received by the institution (and shared with the inventor by law) from licensing of the invention. While the logic behind this approach is understandable, it does not serve technology development well as it creates difficult choices for an investigator and situations that are not optimal for development of early stage technology. While we all agree that our conflict of interest policies serve an important and necessary role, we need to continue to find ways for academic researchers to appropriately work with industry. Guidelines offering approaches to "manage" such conflicts in appropriate ways would go a long way to alleviating this situation.

4. Technology Transfer: Technology transfer offices have traditionally worked on a service and income generating model, with services by and large having the greatest emphasis. There is good reason for this as income generation is largely a happenstance situation that the technology transfer office ultimately does not control (control being in the hands of a licensee/partner company). As a result these offices have been historically funded quite leanly and have limited access to expertise relating to markets, clinical need, technology requirements for competitiveness, regulatory issues and reimbursement issues. However, some offices, due to success, volume of inventions and/or institutional focus, have developed quite specific areas of expertise which could be shared with other offices. However, a model which incentives offices to share expertise has not been developed. The Kauffman Foundation explored this issue and concluded that investigators should be allowed to work with whatever office best suits their needs and the needs of the instant technology. While there are a number of problems with this simplistic approach, the concept of accessing technology transfer offices with specific expertise deserves some consideration. As these technology transfer centers of excellence do exist in different fields, the federal government could fund an initiative to identify these centers and then support a limited effort to explore mechanism of expertise sharing and/or consulting on development of specific technologies identified as having superior clinical potential.

Workforce development

We are facing a crisis with respect to trainees in the sciences. American institutions awarded 25,836 doctorates in the sciences in 2009. The majority of these students will not find positions in academia due to decreasing budgets. While a PhD program is an excellent way to prepare one for a career in research and academia, most programs do a poor job of providing students with the skills to pursue other careers, and in many cases don't provide any information regarding jobs outside of academia. Often these individuals drift away from their scientific roots into unrelated careers. These highly trained individuals are a significant resource that could impact US productivity, inventiveness and competitiveness if provided with the right training.

Viewing the issue from a different perspective, even those select few PhDs or MDs who find positions in academia, have little or no training in entrepreneurship and technology commercialization. The NIH itself has identified as a priority the need to "develop teams of

investigators from various fields of research who can take scientific discoveries and turn them into treatments and strategies for patients in the clinic". In order for this to become a reality, investigator teams must not only understand the basic science/disease physiology, clinical need and clinical trial design but also understand how all these factors impact marketability and technology feasibility. In other words, in order to have a real impact on patient care, investigators should understand the entire development path and critical pressures both financial and regulatory, that will determine whether a particular treatment is feasible. Understanding the complete pathway will not only help in early stage research but will also inform as to what resources and specific knowledge will be critical in assembling the optimal research and development team.

Suggested approach:

1. Postdoctoral fellowship in technology commercialization: The goal of this program would be to provide training to biomedical investigators (MD or PhD) in technology development including instruction and hands-on experience in areas relating to technology evaluation, business assessment, intellectual property protection, and product development including regulatory, reimbursement and market issues.

   While there are a number of aspects of this concept that are already available, there is no single program that provides course-based instruction as well as hands on experience in translational research labs, intellectual property firms and startup companies and/or venture capital. The program would also encompass some career counseling which would allow an amount of "tailoring" of the program to individual interests. In other words, if the candidate were interested in pursuing an academic career, the program would include experience in a laboratory performing translational research as well as shorter rotations in a law firm and/or company. Conversely if the interest were more in the area of intellectual property, the time frame for different rotations would be adjusted appropriately.

   I have conducted a limited amount of marketing research with current PhD students in my institution and in others and they have responded with an overwhelming level of interest. As outlined the program would require cooperation and collaboration with different public and private entities including academic centers, law firms, companies and investment groups. Again limited marketing on my part indicates that there is interest and enthusiasm from the private sector. As envisioned this program sits at the intersection of science and medicine,, law and business. Technology transfer offices also sit at this same intersection and many offices including the Partners Healthcare office have provided informal training through internship programs. This fellowship in technology commercialization could have as its administrative home, one or a number of the technology transfers centers of excellence identified through NIH resources in #4, Moving Life Sciences Breakthroughs (above). Funding for such a program is envisioned as a combination of public/private support.

Public-private partnerships

Public-private partnerships are key to advancing technologies and treatments for healthcare as it is becoming increasingly evident that neither the academy not the private companies have all the expertise and resources needed to achieve effective translation of basic research into safe and effective clinical applications. To date, models of interaction have focused on different ways to bring the relevant

expertise from entities in either camp together in the hopes that proximity will catalyze effective translation. However, academic scientists and industry scientists/engineers work in fundamentally different ways and in many cases appear to speak different languages. There has been little focus on models to bridge this cap, in other words, on effective handoff from one entity to the other. It has been my experience, especially with early stage technologies, that problems in handoff often lead to failure of promising technologies.

Suggested approaches:

1. Technology translators: One approach that is being piloted at a number of academic institutions is to hire personnel with the appropriate background (engineers, chemists etc) and industry experience to work side –by-side with academic scientists. These personnel are experienced in project management and focus on advancing promising concepts through the early phases of R&D. This approach has a number of advantages:
    a. It protects the academic scientist leaving them free to continue to innovate and to pursue more academic approaches and career advancement.
    b. It provides for close coordination with ongoing research allowing the development function to feed back into the basic science efforts to stimulate fresh ideas. This has been termed by some as the "virtuous cycle" – translation stimulating further innovation.
    c. It provides for greater success in raising private funding or in licensing of technologies because it effectively "de-risks" the technology.
    d. It has the potential to accelerate time to market as the technology advancement is conducted by personnel experienced in project management and technology development. The goal would be that the company would not have to repeat any of the development activities as these would have been conducted according to industry standards. Further the development personnel would also function to transfer the technology to company personnel at the appropriate time.

The federal government could play a major role in this effort by helping to bring together the relevant parties. Important in this effort is coordination with the disease foundations as not only do they have access to patients, they also have broad internal expertise and a knowledge of world-wide research and development programs relevant to their disease indication. Coordination of the disease foundations with academia (and academic medical centers) and industry should not only help address the financial constraints but should allow leveraging of all relevant expertise for translation into effective health care.

This is input on how best to develop the National Bioeconomy Blueprint from the Bio-Link National Center based at City College of San Francisco.
The Bio-Link Next Generation National Advanced Technological Education (ATE) Center for Biotechnology and Life Sciences builds on the success of the original Bio-Link National Center for Biotechnology that was first funded by the National Science Foundation (NSF) in 1998. Bio-Link's mission is to 1) increase the number and diversity of well-trained technicians in the workforce; 2) meet the growing needs of industry for appropriately trained technicians; and 3) institutionalize community college educational practices that make high-quality education and training in the concepts, tool, skills, processes, regulatory structure, and ethics of biotechnology available to all students. Currently there are about 100 community and technical college biotechnology programs in the Bio-Link network. This network extends across the country. The website, www.bio-link.org<http://www.bio-link.org> provides an overview of the work of the Bio-Link network.
The following comments address item #10 in the RFI.

What can community colleges do to promote the Biotech workforce for the Bioeconomy?

1. Community College Biotech programs across the country receive valuable technical assistance and support from Bio-Link to create, build and extend their biotech education programs. In order for community college biotech programs to supply enough skilled technicians for the Bioeconomy, it is important for the White House to continue to invest in the 2 NSF ATE Centers focused on Biotechnology: Bio-Link the National Center and NBC2 the Regional Center for Biomanufacturing and to continue support of other related life science ATE projects and centers.

2. To deepen this investment and provide a more robust level of support to community college biotech education programs across the country, the White House could support the funding of 10 regional Biotech Centers ($5 million per Center X 10 Centers X 5 years = $250 million) that would be mentored by Bio-Link and whose activities and efforts would be coordinated through the National Bio-Link ATE Center. This would allow greater levels of activity and development in each of these regions in the areas of biotech program development, industry partnerships, labor market research and career education of prospective students.

3. Community colleges, with the proper resources and technical assistance from Bio-Link , could replicate the most promising biotech experiential learning approachesthat have been developed around the country. These include student internship models, faculty externship programs, Contract Research Organizations (CROs) and Biotech incubators. The White House could support these activities by providing incentives for federal labs and research organizations to create these experiential learning opportunities that are critical to the educational development and employability of biotech students at community colleges. The White House could also create incentives for Biotech firms to create these same experiential learning opportunities as a critical part of ultimately building the Bioeconomy.

4. Community colleges can expand their existing efforts to assist workers in career transition to learn about Biotech careers and enter Biotech training

programs to meet labor market demand. The White House can support these efforts with continued support of TAA and DOL funding initiatives for Biotechnologytraining towards this goal.

5. Community colleges, with support from the White House, could create a national tracking system for employment outcomes of biotech students. We need better data on the success of biotech graduates in the labor market to answer the question: “What is the value of a community college certificate or degree in the labor market?” This data would allow colleges to make the case – we believe - with survey data that their students are employed in the biotech field and that their certificate or degree led to employment at a living wage, with careeradvancement opportunities. This is key to making the case to new students that the bioeconomy is thriving and a good place to look for employment. This will drive new enrollments in biotech education programs and provide these programs with important data to inform their future development.

6. TheWhite House could support Biotech and Life Science credentialing efforts and stackable certificate efforts that are currently in practice for manufacturing technicians.

Contact Information
Elaine A Johnson, PhD
Bio-Link Executive Director

Fri 12/2/2011 8:52 AM
Re: National Bioeconomy Blueprint/DNA Sequencing

Hi Tom,

If you didn't see it, attached is yesterday's NYT article about the DNA sequence data glut. Basically, doing DNA analysis is now like drinking water out of a fire hose --

"The result is that the ability to determine DNA sequences is starting to outrun the ability of researchers to store, transmit and especially to analyze the data". “Data handling is now the bottleneck.” ... “It costs more to analyze a genome than to sequence a genome.”...“It’s not at all clear what you do with (all) that data,” .... “Doing a comprehensive analysis of it is essentially impossible at the moment.”

Clearly, this DNA deficit adversely effects the National Bioeconomy in many different ways.

Originally, we were thinking about doing data discovery with our planned new software product, see attached. We branded this product MetaQor and it uses cloud computing. However, our new system is also a superb tool for very high throughput DNA data sequencing and analysis.

The MetaQor Cloud for DNA data sequencing and analysis could be made available to all Internet users at no or minimal cost, providing a key infrastructure element in the National Bioeconomy--IF we can solve the energy requirements to run the system. Large scale server plants consume huge amounts of electricity and adversely effect the economics. Researching and developing ways to economically solve this problem using alternative energy could make for an interesting, high payoff DOE grant. Would your office or OST have contacts at the DOE with whom I could speak to about this?

Many thanks,

Franco

Franco Vitaliano
President & CEO
ExQor Technologies, Inc.

MetaQor tm

Shortening The Drug Discovery Pipeline

ExQor Technologies, Inc.

Boston MA

About ExQor

ExQor Technologies, Inc. is a multi-disciplinary company, founded in February 2004 in Boston MA, USA.

ExQor is the only company that has fully embraced the National Science Foundation's **NBIC** principles of "Converging Technologies for Improving Human Performance".

NBIC is integrative product approach that unifies **N**anotechnology, **B**iotechnology, **I**T, and **C**ognitive science.

ExQor has developed a unique new model of human cognition based on the brain's dynamic biological and developmental processes, from infancy to adulthood. It is not AI, nor a neural net. It is something totally new in cognitive science.

The product name is MetaQor [tm] and it uses a cloud computing architecture.

ExQor's breakthrough in cognitive science also led to a major biomedical innovation in understanding the central nervous system and how to treat its diseases and disorders.

In one business role, ExQor is developing innovative new large molecule drugs for treating CNS cancer, and also for enhancing CNS neuroprotection and neuroregeneration for treating neurodegenerative diseases, stroke, and traumatic brain injury.

Some of the biomedical research is being done under non-exclusive license at Harvard Medical School (McLean Hospital), and funded by the NIH, NIDA, NARSAD, private foundations, and other funding sources.

ExQor's bio-nanotechnology is broadly protected under multiple issued patents, with additional patents pending in the US and elsewhere in the world.

About ExQor

Franco Vitaliano, President and CEO and ExQor co-founder and co-patents holder, was formerly President & CEO of VXM Technologies, a Boston-based firm that specialized in advanced bio-nanomaterials and novel, network parallel and massively parallel computer architectures for extremely high performance systems.

These systems were based on his more than two decades of work in developing advanced models of human neuro-biosystems and modeling proteins in the brain. VXM's clients included General Motors, Ford, Chrysler, GTE, the U.S. Air Force, the U.S. Navy, MITRE, the NSA, General Dynamics, Sandia National Labs, Argonne National Labs, and the DOT, among other major clients.

At ExQor he conceived and developed the company's unique and extensive bio-nanotechnologies and also formulated its global business strategy.

He also has extensive expertise in formulating global IP/patent strategies, and was primarily responsible for the conceptualization, technical drafting, and successful defense and approval for all of ExQor's patents.

He has served as an expert in bio-nanotechnology at the President's Innovation and Technology Advisory Committee (The White House), and on DOD conferences.

Gordana Vitaliano, M.D., Vice President and ExQor co-founder and co-patents holder, was formerly the Director of the Nanomedicine Lab for Neuroscience at Caritas St. Elizabeth's Medical Center in Boston MA.

She is an NIH grant recipient and sits on NIH review panels for bio-behavioral science. She emigrated from Serbia to the U.S. in 1991 (where she received her medical degree at Belgrade University) when she won a highly prestigious NIH Fogarty Fellowship.

She is currently employed at McLean Hospital (Harvard Medical School) in Belmont MA, where she is designing bio-nanotechnology with the potential to become a powerful tool in medicine, and in the future may lead to the development of diagnostic tools, targeted delivery systems and cellular repair platforms for the CNS.

This nanotechnology research work, for which she has received 3rd party grant support after extensive scientific panel review, involves utilizing ExQor's patented bio-nanotechnology for advanced CNS applications in medical imaging and drug delivery. The work is being done under a non-exclusive license from ExQor.

She has served as an expert in bio-nanotechnology at the President's Innovation and Technology Advisory Committee (The White House), on NIH review panels and on NIDA and DOD conferences.

MetaQor

- Pharma's don't waste time on fruitless compound searches.
- MetaQor does all the work.
- The MetaQor cloud automatically keeps the Pharma abreast of continually changing drug data and requirements in real time.

Current Discovery Systems

- Pharma's run down promising drug leads, only to find they are dead ends.
- What looks like a promising drug emerging from a morass of data is just a phantom reflection of the best compound result.
- The real, meaningful data about the best compound lies buried deep, but current tools are unable to see it.

Current Drug Discovery Systems

- Drug discovery requirements in today's large scale, multi-departmental Pharma environments present highly complex data management challenges.
- High-throughput technologies have created a drug discovery crisis by generating vast amounts of disparate data that must be processed and analyzed.
- A wealth of data are continuously being collected, and in some cases, simulated, including:
  - Historical data
  - New data
  - Lab data
  - Sensor data
  - Analytical data
  - Field data
  - Trial data
  - Third party data
  - Regulatory data

Current Discovery Systems

Only with intelligent, transformational technologies and tools can Pharma's:

- Accurately identify and qualify high value compound targets
- Accelerate new drug development
- Plan effective business strategies
- Rapidly respond to events
- Bring innovative new products to market at the accelerated pace now required.

Challenges in Drug Discovery Systems

Several types of discovery systems are currently available, such as those that use Bayesian or probabilistic models, neural networks, etc. Each has their strengths, but they also have notable deficiencies, below.

Neural Networks

- The performance of a neural network can be sensitive to the quality and type of preprocessing of the input data.
- The most commonly used methods for training neural networks are well-known to have difficulties with local minima (trapping in sub-optimal solutions); these can be demonstrated to occur even for simple problems such as XOR, requiring a network with only a few neurons. Worse, the more efficient the algorithm (moving for example from error backpropagation to conjugate gradient descent) the more likely the algorithm is to be trapped in a local minimum.
- Neural networks cannot explain the results they obtain; their rules of operation are completely unknown.
- Performance is measured by statistical methods giving rise to distrust on the part of potential users.
- Many of the design decisions required in developing an application are not well understood.

Bayesian Models

- Bayesian results cannot be averaged, added, etc.
- There is the computational difficulty of exploring a previously unknown network. To calculate the probability of any branch of the network, all branches must be calculated. While the resulting ability to describe the network can be performed in linear time, this process of network discovery is an NP-hard task which might either be too costly to perform, or impossible given the number and combination of variables.
- A Bayesian network is only as useful as this prior knowledge is reliable. Either an excessively optimistic or pessimistic expectation of the quality of these prior beliefs will distort the entire network and invalidate the results. Related to this concern is the selection of the statistical distribution induced in modeling the data. Selecting the proper distribution model to describe the data has a notable effect on the quality of the resulting network.

Discovery Challenges & Solutions

- To overcome current drug discovery limitations and produce a successful method, we leverage ExQor's deep expertise in cognitive development and developing new CNS drugs. We apply this collective knowledge to an innovative, robust discovery method that produces global results faster, better, and more intelligently than any other drug discovery approach currently available.

- To solve the problem of fusing large, multi-attribute data sets, ExQor has undertaken the development and implementation of an algorithm based on human cognitive functioning, which has several unique characteristics that make it ideally suited and superior to other kinds of drug discovery solutions. The end product is called MetaQor tm

MetaQor

- **Self-knowledge**—Can identify its purpose and understand its internal functions.
- **Perception**—Has the ability to recognize, interpret, and understand highly complex sensory inputs.
- **Reasoning**—Capable of making intelligent, autonomous decisions based on its perception of the environment and carrying out tasks to successful completion by using its own initiative.
- **Cognition**—Its intellectual processes include all aspects of knowing, such as awareness, perception, reasoning, and judgment

MetaQor Transforms Discovery

The MetaQor cloud best uses the information in *ALL* of the drug data.

- There is no hidden layer problem as in neural networks.
  - ✧ All MetaQor operations are exposed.
- Unlike Bayesian approaches:
  - ✧ MetaQor results can be averaged, added.
  - ✧ NP-hard tasks are avoided that are either too costly to perform, or impossible given the number and combination of variables
  - ✧ Validates prior knowledge with new knowledge

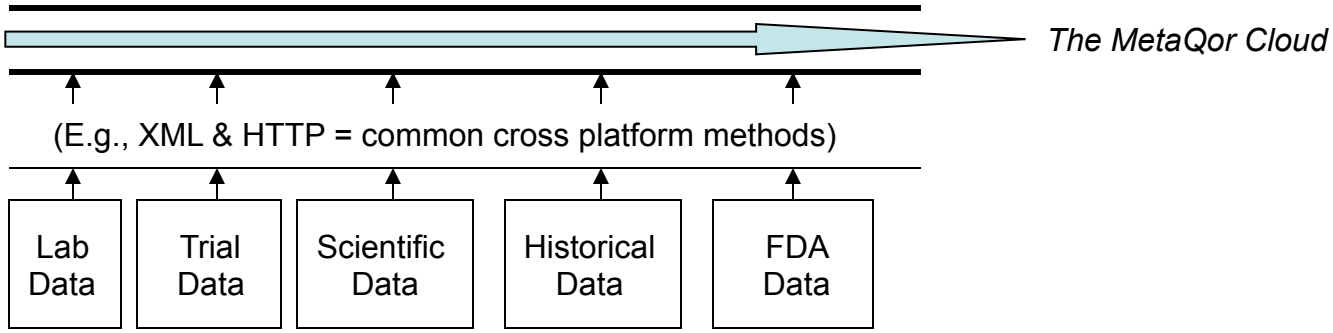
MetaQor Transforms Discovery

MetaQor capabilities include:

- ✧ Altering searches based on its own "outside" observations or interpretations.
- ✧ Cognitively categorizing new and old drug data based on prior results.
- ✧ Deciphering incomplete or inaccurate data by considering it in conjunction with related information and human judgment.
- ✧ These are human *cognitive functions* replicated in MetaQor.

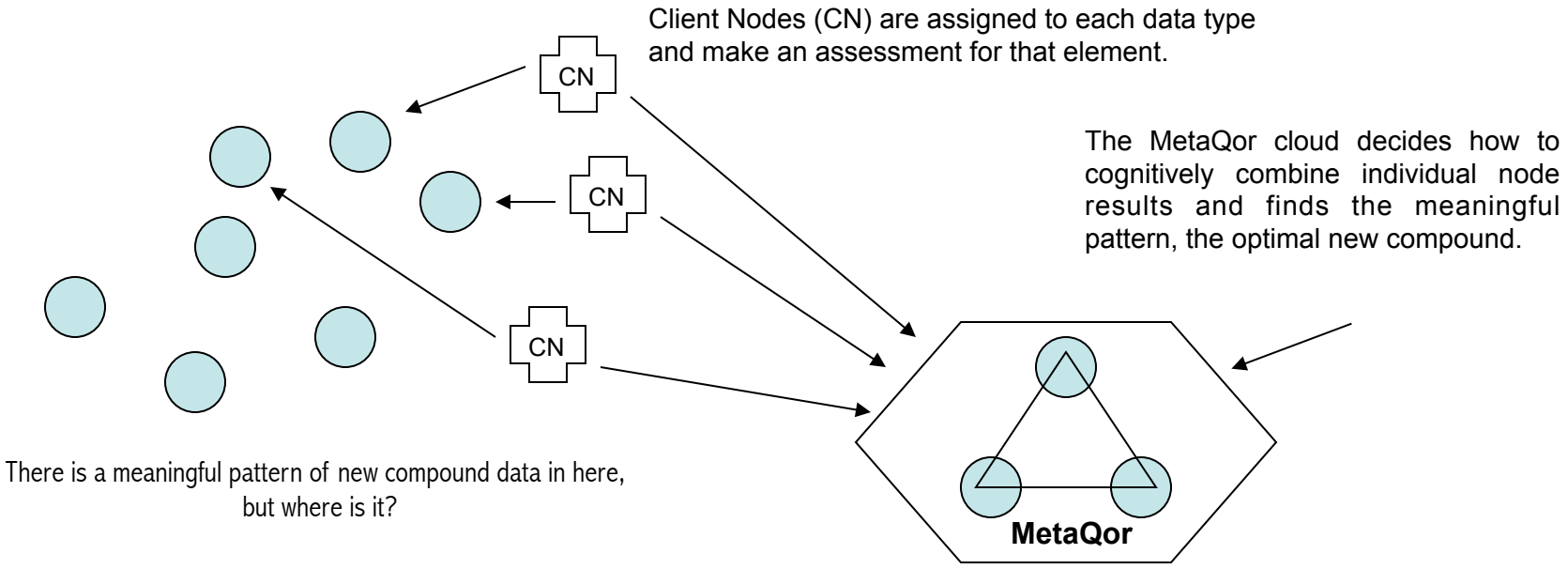
MetaQor Architecture

- The MetaQor Cloud can handle vast quantities of heterogeneous data in real time, which allows seamless integration of the multitude of point applications that have sprung up and captures multi-workflows for analysis, design, deployment, and compliance reasons.
- The MetaQor Cloud is a computational approach to managing the exchange of information among various data sets in order to maximize both the flexibility for addressing unexpected data types and for introducing both human and machine insight.



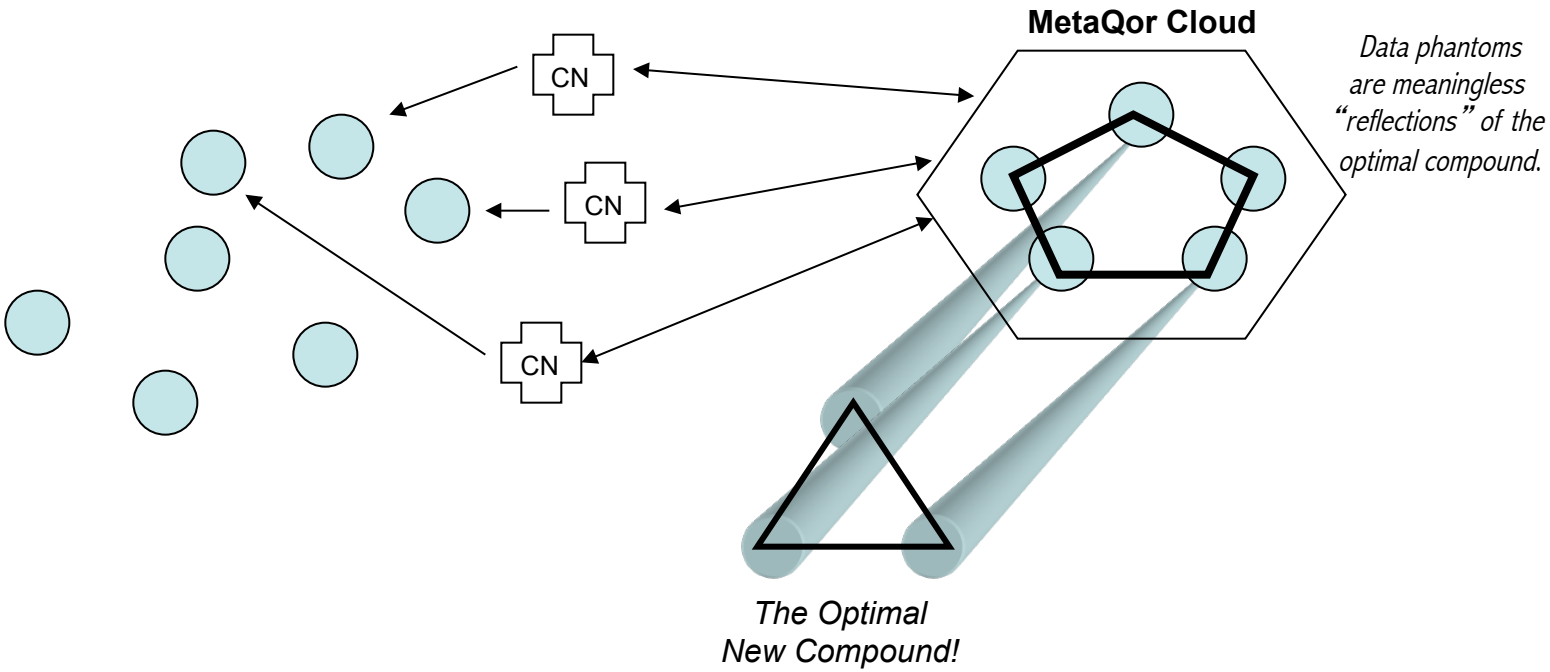
MetaQor At Work

- The advantages of MetaQor derive from a unique architecture that globally coordinates and optimizes the states determined by its client nodes, which can run on local systems or operate anywhere worldwide via the Internet.
- Each MetaQor client has only partial access to new and old data that may be remotely distributed, be intermittently or newly available, or represent interactive human interpretation.
- The MetaQor cloud combines individual client findings into one global, cognitive discovery of a new compound that best uses the information in ALL of the data.



MetaQor At Work

MetaQor saves Pharma's wasted years chasing after phantom leads.



MetaQor Workflow

This workflow in the MetaQor cloud can be explained in more detail as follows:

- Each piece of drug data anywhere on the network is processed according to its data type.
- Client information is sent back to the MetaQor cloud that employs a cognitive algorithm.
- It is the job of the MetaQor cloud to cognitively determine the optimal overall results in order to make the best global assessment of all the data in the entire system.
- The MetaQor cloud will iterate back to its distributed clients and share relevant information about the states of the other data types until optimal discriminate variables are achieved, and a global, cognitive discovery of the optimal drug compound is made.
- The MetaQor cloud allows the exchange of information between data types without requiring them to be translated into the same format. Moreover, data classification and drug discovery can be improved by using previous results or by introducing additional related information.

MetaQor

Key Characteristics

- Cognitive mastery of logical operations is not obtained all at once, but by degrees of comprehension determined by the complexity of the structure of the logical operation.
- Also, computational ability, defined as the number of terms and relations that may be computed simultaneously, increases with maturation and development.
- However, cognitive mastery of logical operations is not only a matter of mere computational power.
- It also involves strategies and rules for the cognitive organization of information.

MetaQor

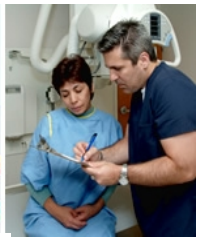
Key Characteristics

- MetaQor is an all-software tool.

- MetaQor breaks down the barriers to writing powerful parallel processing applications, heretofore a huge hurdle. In addition, you also get powerful cognitive capabilities.

- Thus, a unique new capability for drug discovery:
  - Executes in parallel.
  - Employs and integrates multiple types of search strategies.
  - Performs very complex searches across disparate, distributed old and new data.
  - Continually refines its queries, scores and ranks hits based on its growing self-knowledge, perception, reasoning and cognitive faculties.
  - ⊙ There can be multiple types of cognitively cooperating MetaQor clouds in a global Pharma network, forming a new type of Internet Cloud, a Cognitive Meta-Cloud.

Multiple MetaQor Clouds = Internet Meta-Cloud = Global Pharma Productivity



MetaQor Cognitive Clouds

- Secure Unification
- Integrated
- Analyzed
- Contextualized
- Customized
- Real Time

Self-Aware

MetaQor Cloud

(XML, etc., + HTTP = common cross platform methods)

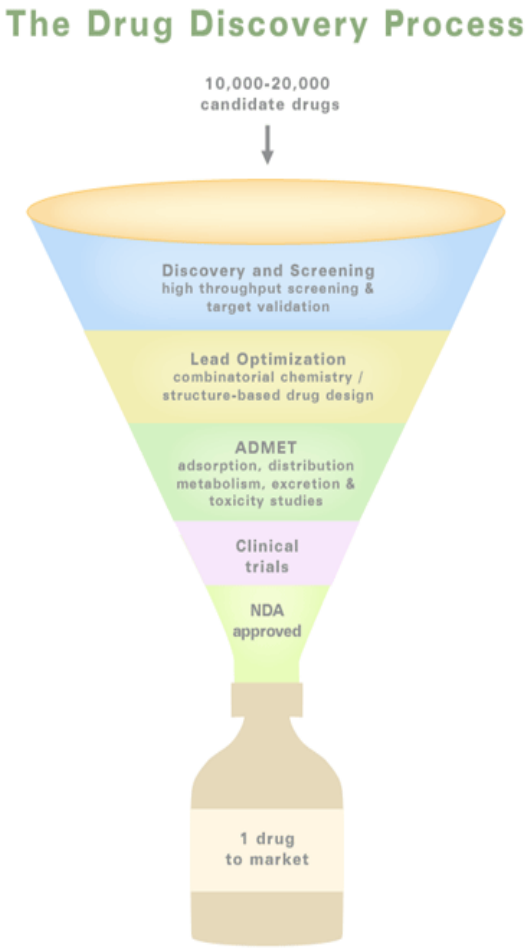
Provider Data | Industry Data | Scientific Data | Financial Data | Medical Data | Patient Data | Government Data

MetaQor

SUMMARY

MetaQor enables an easy, fast and reliable way to find meaningful real-time drug discovery results from distributed, disparate data.

- No more fruitless drug discovery searches.
- No more chasing after drug compound phantoms.
- MetaQor does all the work.
- MetaQor thrives in an environment of continually changing data and requirements.
- All these MetaQor benefits go straight to the Pharma's bottom line.



MetaQor ™ for Drug Discovery

ExQor Technologies, Inc.
Four Longfellow Place, Suite 2105
Boston MA 02114 USA

Tel 617 742 4422
Contact: Franco Vitaliano
francov@exqor.com

Office of Science and Technology Policy

Request for Information: Building a 21st Century Bioeconomy

December 2, 2011

The Council of Graduate Schools (CGS) is pleased to provide input to the Administration's National Bioeconomy Blueprint detailing steps to harness biological, research innovations to address challenges in health, food, energy and the environment. Among other things, this Blueprint will identify strategies to meet the grand challenges, focus research and development investments in areas that will provide the foundation for the bioeconomy and expand workforce training to prepare the next generation of scientists and engineers for the bioeconomy jobs of the future.

Our comments focus on the elements of the request related to workforce development and investments in education and training that are essential to creating a technically-skilled 21st century American bio economy workforce. We first provide information on recent reports concerning the role of graduate education in preparing a highly skilled workforce and the need to prepare more graduate students for careers beyond the academy. Specific comments and recommendations related to workforce issues in the RFI follow our general comments.

Background:

In 2010, CGS and Educational Testing Service (ETS) released a report titled *The Path Forward: The Future of Graduate Education in the United States.* That report provided a comprehensive overview of the trends, challenges, and vulnerabilities existing in the current U.S. system of graduate education and described the importance of producing an adequate number of graduate degree holders to meet 21st century needs. Pressing issues facing graduate education include:

- Demographic shifts that present educational challenges including lower levels of education particularly in math and reading skill levels.
- Disruptions in pathways to and through higher education complicated by drop-out rates at both the high school and undergraduate levels.
- Growth in international education and career opportunities for both international students and U.S. students.
- Failure to complete a graduate degree is one of the most vexing problems confronting U.S. graduate education, particularly at the doctoral level.
- Accumulated debt is consistently identified as one of the most important concerns of graduate deans and inadequate financial support is the most significant factor contributing to a student's ability to complete the doctoral degree.
- Career path transparency in terms of clear career pathways for graduate degree holders are often lacking, especially at the doctoral level. This lack of knowledge impacts students before they enter graduate school, during graduate school and upon degree completion.

Universities, businesses and government are responding to these challenges in a variety of ways. Through the Ph.D. Completion project, a number of universities have been working to improve completion rates at the doctoral level for a decade with some success. More information about the Ph.D. Completion project is available

at http://www.phdcompletion.org/. Several recent federal policy initiatives, including the COMPETES Act, recognize the role of graduate education in preparing a highly skilled workforce and an educated citizenry and authorize financial and programmatic support accordingly. Many business leaders and corporations are actively engaged with universities and graduate schools to enhance communication concerning workforce needs, to provide internship and research opportunities, and in some cases financial support for graduate education and research.

Amongst the many issues, challenges and responsive activities addressed in the Path Forward report, one question emerged as critical to ensuring graduate schools are preparing precisely the talent that America needs. How effectively are America's graduate schools and America's employers working together to ensure the optimal pathway through graduate school and into careers? This issue has several dimensions. The critical dimension relates to student knowledge about career pathways and the programs that lead to careers in the 21st century global economy. Another aspect of the issue concerns the need to have a better understanding of the country's future workforce needs in critical areas including the next generation of scientists and engineers for the bioeconomy jobs of the future.

Commission on Pathways through Graduate School and Into Careers

Earlier this year, CGS and ETS launched a new *Commission on Pathways through Graduate School and into Careers* that will offer findings and policy recommendations in a new report to be released in April 2012. The Commission, composed of distinguished corporate and university leaders, is guiding a research effort addressing issues that include graduate student knowledge of career options, how students learn about occupational opportunities, the role of graduate programs and faculty in guiding students along the path to professional occupations, and career pathways that individuals with graduate degrees actually follow. We believe this new initiative and forthcoming report will be of interest to OSTP and other federal agencies when it is released. The press release announcing the Commission is available at the following link:
http://www.cgsnet.org/portals/0/pdf/N_PR_PathwaysCommission_Sept2011.pdf

The Pathways Commission has met twice to date to discuss the importance of developing a better understanding of how students make decisions about careers and the need for stronger and more deliberative linkages between graduate education and employers in industry, government and non-profit sectors. A clear theme emerging from the Commission's ongoing research effort is the need to prepare more graduate students for careers beyond the academy and specifically for careers in industry and government. Research conducted by some disciplinary societies has focused on the need to prepare more graduate students for careers outside of the academy.

For example, a recent study found that two-thirds of chemistry Ph.D.'s work outside of academe. Thus, calls for reorientation and revitalization of doctoral education in the field of chemistry have been made to include graduate preparation in teaching, teamwork, leadership, and management roles in and out of academe. Beneficial practices and strategies to support such preparation may include implementation of improvements to curriculum, advising, interdisciplinary training, internships, career preparation, outreach, and recruitment and retention of more diverse students. A key issue for further exploration is the development of holistic and scalable approaches to the training of graduate students in chemistry, as well as other fields to prepare independent, analytical thinkers with transferable skills. (Journal of Chemical Education 2011, 88.708-715. Reactions to Changing Times: Trends and Tensions in U.S. Chemistry Graduate Education.)

There are also many examples of collaborations between industry and graduate schools to provide training and information to graduate students about careers in certain sectors or corporations.

For example, Microsoft operates the largest Ph.D. internship program in the information technology industry. Each year, nearly 1,000 top computer-science students have the opportunity to work at one of the Microsoft Research's locations around the world. (Ideas. Intellect. Innovation, Microsoft Research, 2010)

These examples, while not specific to biological research training, are relevant in terms of providing future researchers with the types of transferable skills needed to be successful in most professions in the future.

The RFI states – ***the majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bio economy jobs?***

The biological research and development workforce of the future requires people with the knowledge, skills and flexibility to work at the interface of disciplines. In addition to intensive training in biological research, the professional training required for the future biological workforce will have much in common with the type of training needed for graduate students in a variety of other fields.

The Commission on Pathways through Graduate School and into Careers has identified some preliminary ideas and proposals to prepare graduate students for a variety of 21st century careers as follows.

Graduate Schools are at the forefront of providing graduate education and training in the biological research and development areas. Many universities are engaged in providing graduate students with opportunities to engage in research and internships in the corporate and government sectors but more institutions need to do this. Universities have a responsibility to graduate students to provide them with information about a variety of career pathways beyond those in academia and to note the opportunities for career fulfillment and success in these sectors. Many universities utilize graduate alumni from biological fields to showcase career pathways in different sectors for graduate students and this initiative needs to become a hallmark of graduate education in the biological research area as well as others.

Additionally, many Graduate Schools offer Preparing Future Professional (PFP) programs designed to allow students to explore opportunities in business, government and non-profit organizations and to enhance their preparation for those career options. Rooted initially in the Preparing Future Faculty program, the PFP programs address a range of transferable skills. Active programs can be found at Arizona State University, the University of Texas, Michigan State and Virginia Tech.

Increasingly, universities are creating advisory groups of employers to provide input and perspective on the types of training and skills needed for 21st century jobs in the bio economy. The creation of advisory groups is a cornerstone of Professional Science Master's (PSM) programs. The predominant field of study for existing PSM programs is biology/biotechnology reflecting its importance to the nation's future.

Employer advisory groups should be a hallmark of all graduate education programs in the biological areas, as well as others, at both the master's and the doctoral levels to help inform the curriculum and structure of graduate education and the production of future researchers and leaders prepared for jobs in the bioeconomy.

Faculty serve as mentors and advisors to graduate students, particularly at the doctoral level. Another effective strategy involves providing sabbaticals for faculty to conduct research or work in industry/government/non-profits to provide them with direct knowledge and experience of workforce needs and the types of knowledge, skills and training needed by future professionals. These types of sabbaticals should become more widespread and would be beneficial in the preparation of the future bioeconomy workforce.

What role should the private sector play in training future scientists and engineers for the bio economy?

Industry and non-profit organizations are in the position to signal the knowledge and skills necessary for success in non-academic sectors. Increasingly, employers across these sectors indicate a need for professionals who excel in teamwork, communications, problem identification and solutions and ability to have a broad view. Many professionals from these sectors serve as adjunct faculty for graduate students and this is a practice that could be expanded to enhance communication and collaboration between graduate school faculty and potential employers of people with graduate degrees in bio fields.

Industry in particular is in the position to fund biological basic research to provide a platform for advances and discoveries in health, food, energy and the environment. Federal agencies and biology oriented businesses could consider enhanced investments in university-based basic research that would support the training of graduate students. The IT industry provides an example with the commitment of Intel to invest $100 million over five years in universities to fund about a half dozen campus centers that will focus on research in computing and communications.

What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students and postdocs?

Past discoveries and breakthroughs in the biological areas as well as others have been the result of entrepreneurship and risk-taking. The federal government is in a position to encourage entrepreneurship and risk-taking through support of new initiatives focused on addressing current national challenges in the bioeconomy. The federal government should give funding priority to proposals that fund collaborations between universities, businesses and government/non-profit organizations working on addressing national bioeconomy challenges.

The federal government should consider implementing a COMPETES doctoral traineeship program that would support doctoral education in areas of national need including biological research by providing direct student support through a stipend, tuition and fees, ancillary fringe costs, and other costs of education. Funds would be provided in response to proposals submitted by universities for graduate programs to support doctoral students in key areas. Those submitting proposals would be required to provide data, including enrollments, completion rates, and job placement information to the funding agency as part of the ongoing accountability associated with this funding. They would also demonstrate the institutional capacity to offer professional skill development of the kind offered to students in strong PFP programs. More information about the COMPETES Doctoral Traineeship program is available at http://www.fgereport.org/rsc/pdf/CFGE_report.pdf

Thank you for the opportunity to provide input to OSTP concerning the development of a National Bioeconomy blueprint including the development of the future workforce that would support biological research and innovations. Please contact Patricia McAllister at 202-223-3791 or at pmcallister@cgs.nche.edu for additional information.

Sent: Fri 12/2/2011 1:20 PM

Subject: Bioeconomy RFI

High-impact actions needed to support a bioeconomy:

Education and training of graduate students.
Foundational tool development for engineering biology
Bio-manufacturing materials
Application oriented approaches for expanding the chemistry of life/biology.

Thanks,
Mike

--
Michael C. Jewett

Assistant Professor
Department of Chemical and Biological Engineering
Chemistry of Life Processes Institute
Member, Robert H. Lurie Comprehensive Cancer Center
Northwestern University

ADVISORY COMMITTEE FOR

Biotechnology in the Piedmont Triad

A PARTNERSHIP OF PIEDMONT TRIAD CITIZENS AND THE NORTH CAROLINA BIOTECHNOLOGY CENTER

The Piedmont Triad is pleased to provide this information in response to the BioEconomy Challenge request for information. The input is based on North Carolina's success with building a life-science cluster.

The items listed below are not in order of importance and have been formatted as bullet points.

- Establish an FDA committee of academic and corporate leaders, including those from medical device, diagnostics and theranostics companies, to collaborate on the development and refining of predictive modeling programs for drug safety and efficacy. This could help reduce untoward side effects, costs and time from discovery to the marketplace.

- The FDA should:
    - (a) review list of FDA-approved indications for which INDs, clinical trials, and NDAs can be filed/conducted,
    - (b) review FDA-approved primary and secondary endpoint/outcome metrics. Researchers at prominent academic institutions are developing methodologies for measuring clinical trial results, but the FDA may not be coordinating with them.

- Establish an FDA subcommittee involving FDA clinicians/statisticians, academic researchers and life-science company chief medical officers to address unmet medical needs.

- To spur workforce development and economic growth, the federal government should establish a grant program to enable academic institutions to fund scientific/engineering internships at life science companies. This will broaden opportunities and stimulate interest in STEM education and provide win-win outcomes for students and life-science companies. The North Carolina Biotechnology Center's undergraduate and industrial (postdoctoral) fellowship programs are examples of successful models.

- With the assumption that life sciences companies prefer to hire locally, an obvious source for talent (i.e. laboratory technicians) is the community college system. The Associate of Applied Science degree programs at community colleges can be taken to the next level, particularly in nationally certified/credentialed programs, through federal reimbursement of tuition and related expenses directly to community colleges (subject to certain restrictions) for displaced workers receiving unemployment compensation who are seeking career changes into life sciences. This would help create jobs and provide a workforce-ready pool of talent.

- Encourage commercialization of new technologies through loan programs in the $100,000 to $250,000 range that don't require personal collateral such as the family home of an academic scientist or entrepreneur in loan guarantees, and simplify application forms.

- Advance the NIH initiative to establish a national translational research center/institute that can spur commercialization of basic university research discoveries via grants and other funding.

- Repeal that portion of the Patient Protection and Affordable Care Act which will institute a 2.3 percent federal tax on medical device company revenues in 2013.

- Support certification programs in development: Certification of specialized skill-sets affirms a knowledge and experience base for practitioners in a particular field, their employers, and the public at large. Working with partners at the national and state level, we aim to advance a process of adapting existing, or if necessary, creating the required certification for the biosciences technical workforce. (National Center for the Biotechnology Workforce, a NC BioNetwork Center, and the National Association of Manufacturers)

Sent: Fri 12/2/2011 3:35 PM
Subject: Comment - National Bioeconomy Blueprint

To: The Office of Science and Technology Policy of the United States

I wish to provide the following comment in response to the posted RFI - Building A 21st Century Bioeconomy:

A safe and sustainable supply of food and water is irrevocably one of the greatest bioeconomy challenges facing the world today. Global demands for high quality protein, scientific awareness of the health benefits associated with omega three fatty acids, and the status of depleted wild fish populations clearly indicate a need for increased food production from aquaculture. As shown by our national seafood deficit in excess of $10 billion, the majority of which is obtained from Asia, the US clearly lags far behind international efforts aiming to increase seafood production. Not only would a major expansion of the US seafood industry boost our economy, it would also help ensure that food and water consumed by Americans is safe, nutritious, and produced by sustainable methods.

Focusing research and innovative technology towards sustainable food production can be accomplished by placing a higher directive, and making more resources available, to Land Grant Institutions and USDA specifically for purpose of sustainable seafood industry development. In order to effectively overcome this challenge, three principles of sustainability must be addressed: long term environmental sustainability, social acceptance, and long term economic benefit. Moving life science breakthroughs from lab to market requires a more programmed and planned effort to bring researchers, industry, and society together to work towards these common goals.

In closing, food and water are the two most critical issues facing societies around the globe. The reality of the situation is, that if we do not place a higher priority on sustainable and efficient agriculture practices under fair regulatory controls, then hunger, poverty and environmental stability will continue to worsen in a growing population.

Sincerely,

Chris Weeks, PhD
Michigan State University
Aquaculture Extension Specialist, North Central Region

---- Advocate for Sustainable Aquaculture Practices ---------

advancing the life sciences 1912-2012

FASEB
Federation of American Societies for Experimental Biology

301.634.7000
www.faseb.org

9650 Rockville Pike
Bethesda, MD 20814

Now representing over 100,000 researchers and scientists

The American Physiological Society (APS)

American Society for Biochemistry and Molecular Biology (ASBMB)

American Society for Pharmacology and Experimental Therapeutics (ASPET)

American Society for Investigative Pathology (ASIP)

American Society for Nutrition (ASN)

The American Association of Immunologists (AAI)

American Association of Anatomists (AAA)

The Protein Society

Society for Developmental Biology (SDB)

American Peptide Society (APEPS)

Association of Biomolecular Resource Facilities (ABRF)

The American Society for Bone and Mineral Research (ASBMR)

American Society for Clinical Investigation (ASCI)

Society for the Study of Reproduction (SSR)

Teratology Society

The Endocrine Society

The American Society of Human Genetics (ASHG)

Environmental Mutagen Society (EMS)

International Society for Computational Biology (ISCB)

American College of Sports Medicine (ACSM)

Biomedical Engineering Society (BMES)

Genetics Society of America (GSA)

American Federation for Medical Research (AFMR)

The Histochemical Society (HCS)

John P. Holdren, PhD
Director
Office of Science and Technology Policy
Executive Office of the President
725 17th Street Room 5228
Washington, DC 20502
Phone: 202.456.7116

Dear Dr. Holdren:

The Federation of American Societies for Experimental Biology (FASEB) is composed of 24 science and engineering research societies with a combined membership of over 100,000 individuals. We wholeheartedly agree with President Obama and the Office of Science and Technology Policy (OSTP) that advances in biological research hold the to key the health, food, energy, environment, and security challenges facing this nation and others around the globe. FASEB appreciates your solicitation of our advice in the development of the National Bioeconomy Blueprint.

The Request for Information (RFI) on "Building a 21st Century Bioeconomy" poses 17 questions covering a wide range of critical issues. Our recommendations for the Bioeconomy Blueprint are presented in detail below and draw upon an active program of policy development undertaken by FASEB on behalf of its member societies. FASEB's responses reflect six major themes:

- **Focus federal priorities on investigator-initiated basic research**. We recognize that the federal agencies are under unprecedented funding constraints and can no longer fund all of the highly meritorious proposals that they receive. Priority should given to programs that unleash the creative potential of scientists and engineers across the nation whose pioneering work has been the source of major discoveries in biology. Because it is hard to capture the return to basic research investment in the short term, only the federal government is in the position to fund the wide ranging, exploratory studies needed to push the frontier of science.
- **Support the efforts of basic scientists who take a more active role in the downstream development of their work**. While not all basic researchers can or should become translational or clinical researchers, they can contribute a tremendous amount to the development of new therapies and products. Indeed, many are actively engaged in such endeavors. Innovation can be expedited by expanding these efforts. We are currently in the final stages of preparing a major report on how to support and extend such activities.
- **Eschew strategies that divert funding from competitive research budgets**. In this time of scarce resources, it is important to ensure that federal funding is allocated to the most meritorious proposals. While there are many worthy proposals and a growing need for research support of all types, the competitive research programs of NIH, NSF, and other research agencies are the backbone of our scientific and engineering enterprise.

They should not be compromised for targeted, goal-directed research.

- **Provide greater flexibility in agency rules for use of SBIR/STTR funding.** Current policies limit the ability of agencies to fund larger SBIR/STTR projects and to transfer funds across program categories. Greater flexibility would be more helpful than increased set-aside targets, which come at the expense of other, valuable research needs.
- **Help graduate programs in the biological sciences provide more opportunities for students to develop a broad range of career relevant skills and experiences.** We have been strong supporters of this concept for many years, advocating expanded opportunities for skill development, greater flexibility in funding rules, and evaluation of training outcomes. Moreover, we have actively promoted the use of Individual Development Plans (IDP) to assist students and their mentors in the identification of the optimal training pathway for each person.
- **Increase efforts to reduce unnecessary regulatory burdens that decrease the productivity of researchers.** We appreciate that the Administration has undertaken several initiatives to streamline, harmonize, and reduce regulatory requirements. These efforts are commendable, and we will continue to provide guidance and support.

In the following section, we present our responses to questions 1, 2, 5, 6, 9, 13, and 15. As our membership is composed primarily of researchers, we confine our comments to the area of our strength and expertise. In addition, we have encouraged our member societies to submit their own discipline-specific comments on these and other questions.

Responses to Questions for Bioeconomy Blueprint

(1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

We are a federation of 24 independent societies, each dedicated to advancing an important area of biomedical research. We have responded to this question in two ways: 1) identifying overarching principles and 2) collecting the proposals from our member societies.

Our April 7, 2010 submission to OSTP outlined our consensus recommendations for investment in biomedical research:

- Sustain support for investigator-initiated research to foster innovation
- Maintain a balanced portfolio of basic, translational, and clinical research to ensure a vibrant pipeline of discovery
- Increase and sustain investment in research training and early-career opportunities to nurture the scientists and engineers of tomorrow
- Assess the cyberinfrastructure investments that will be required to meet the grand challenges
- Ensure access to patient-consented electronic health record data to maximally leverage healthcare information technology investments; acknowledge the value of the use of animal models in research as crucial for the achievement of health-related grand challenges
- Reduce regulatory burden to encourage scientific and engineering progress and
- Institute visa policies that support international exchange and collaboration, while protecting national security.

On September 9, 2010, we submitted a detailed list of proposed challenges solicited from our member societies. The full set of statements is available on the FASEB website.

(2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

It is regrettable that, in a time of great scientific progress and unprecedented opportunity, our nation is forced to limit its investment in research. If we are unable to marshal the resources, then the benefits from increased investment may not be realized or may be captured by other nations. Faced with the need to set priorities, we strongly urge OSTP and the President to maintain funding for investigator-initiated basic research.

A strong emphasis on investigator-initiated research has been the cornerstone of U.S. leadership in science. End-users have motivation and incentives to sponsor applied research, but only an enlightened organization with a long-term horizon can afford to sponsor a broad-based, long term program of investigator-initiated basic research. At this time, only the federal government is able to assume this vital role.

Major advances in treatments against cancer, heart disease, HIV/AIDS, cystic fibrosis and countless other maladies were largely the products of long-term investments in investigator-initiated research. Unpredictable boom and bust funding cycles and a decline in the availability of investigator-initiated research support have made researchers and peer reviewers reluctant to pursue riskier but potentially innovative research directions. In order to nurture the technical and conceptual innovation envisioned by the Administration, there must be ample support for investigator-initiated basic research.

(5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

This is an important topic, one that has generated many proposals for drastic and dramatic action. It should be noted, however, that the much discussed “empty pipeline” has recently rebounded. Nonetheless, all of us would like to see the process improved. One important way to make this happen is to increase the involvement of basic researchers in translational and applied research. To this end, FASEB sponsored a major symposium, “Engaging Basic Scientists in Translational Research.” This two day meeting brought together researchers, administrators, and students to discuss the barriers to greater involvement in translational research and to propose solutions. A final report—with recommendations on funding and training for basic scientists with an interest in translation; facilitating collaborations between basic and clinical scientists in academe and industry; and optimizing publication, tenure, and promotion policies so as to provide appropriate recognition and rewards for translational scientists—is being prepared for release in early 2012.

(6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs[2] would help accelerate commercialization of federally-funded bioeconomy-related research?

Research agencies like NIH should have greater flexibility on how to use funds designated for the SBIR/STTR programs. The limits on the size of individual awards have not kept pace with the rising cost of research, and some meritorious SBIR projects are often underfunded while the agency is required to fund work with lower priority scores in order to meet set-aside levels. Arbitrary limits on funding for phase I and phase II projects are especially problematic for research requiring clinical testing. Rules defining eligibility for these programs should also be revisited, and NIH should have more flexibility to move funds around ***within*** the SBIR/STTR budget.

FASEB supports the SBIR program and recognizes the benefits of the participation of small businesses in scientific research. We do not believe, however, that there is evidence to support an increase in the SBIR/STTR set-aside. The percentage of the NIH extramural funds going to for-profit entities has increased over the past 25 years. During the 1980s, fewer than two percent of NIH research funds went to for-profit firms. This fraction rose to three percent in the late 1990s and has been four percent or greater since 2004.

At present, small (and large) businesses can compete for almost all NIH funding mechanisms. We note that there is currently no limit on SBIR funding. NIH has the discretion to fund all meritorious SBIR applications and, if the submissions warrant it, can allocate more than the current set-aside level, which is 2.5% of the agency's total budget. However, a mandatory increase in the set-aside across agencies will necessarily result in funding cuts for the other peer-reviewed basic and applied research programs that fuel innovation, improve quality of life and contribute to our country's economic growth. Rather than increasing support for one area of research at the expense of all others, we support increased funding for all research agencies, thereby increasing the total investment in SBIR and other projects.

(9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

It would be a huge mistake to drastically disrupt a research training enterprise that is the envy of the world. At the same time, the system that was created for the postwar baby boom generation is in need of change, and we support this effort. The percentage of biomedical scientists in academic employment has been declining, and we expect that trend to continue. FASEB has been actively engaged in the dialog to improve the educational experience of graduate students and postdocs.

FASEB believes that the goal of biomedical training programs should be preparation of trainees for careers in the biomedical sciences, including for positions in research, science education, and science-related fields for which their research training makes them especially qualified. Scientific training should be broad-based, enabling students to pursue a wide range of scientific questions and to transition among research areas as opportunities emerge. It should also incorporate training in teaching and mentoring and preparation in professional skills, such as leadership, management, and communication.

Federal agencies could encourage effective training in all of these areas by expanding programs to help trainees and established investigators acquire training and mentoring skills, encouraging institutions to provide teacher and mentor training to students and postdocs supported on training grants, and providing funding for institutions to develop professional skills workshops. In addition, agency policy should allow all trainees—regardless of their source of funding—to devote time to these activities in the course of their research training.

It is important for funding agencies and institutions to assess the effectiveness of their training and career development efforts. We encourage NIH, NSF, and all federal science agencies to continue to evaluate their programs, including the impact they have on increasing the diversity of the biomedical research workforce. Agencies should also help institutions measure the impact of their programs by developing instruments to measure program success and providing them with funding to conduct program assessments.

For years, FASEB has championed the use of the Individual Development Plan (IDP) as a tool for mentors and students to use in identification of career goals and planning. Our leadership and staff have worked with many organizations and institutions to advise young scientists, and we are currently developing an interactive, web-based tool that will facilitate and enhance the use of IDPs.

We have been in an active dialog with the NIH Advisory Committee to the Director Working Group on the Future Biomedical Research Workforce chaired by Shirley Tilghman. In our official comments to the Tilghman Committee, we recommended that NIH:

- Evaluate the success of its training programs and consider how well trainees have been prepared for a broad range of scientific and science-related careers, not just careers as an NIH-funded investigator.
- Encourage grantee institutions to establish or expand career and professional development programs. These programs should be available to a large number of trainees and focus on the development of core competencies, including problem solving, teamwork, leadership, management, communication, professional conduct, and responsible conduct of research.
- Develop, or fund the development of, training materials that institutions could use in training programs, courses, and workshops aimed at cultivating these core competencies.
- Encourage funded investigators to develop a plan for training and mentoring graduate students and postdoctoral scholars supported on their research grants. Ideally, these plans would address how trainees would acquire the scientific knowledge and technical skills relevant to their disciplines, as well as training in the competencies listed above.
- NIH should encourage trainees to develop, in coordination with their research mentors, individual development plans in which they identify short- and long-term career goals and articulate a plan for meeting them.
- Continue to emphasize that postdoctoral scholars are trainees and should be provided with career and professional development training as well as training in research.
- Issue guidance clarifying that trainees supported on research grants can devote effort to career and professional development activities.

(13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

Unnecessary regulations and reporting are costly to institutions, decrease the productivity of researchers, and delay innovation. In a survey conducted by the Federal Demonstration Partnership , U.S. scientists estimated that 42 percent of the time they spent on federally funded research was devoted to administrative and regulatory activities. This results in the expenditure of $97 million in salary support for principal investigators and co-investigators for activities related to grants administration – not research.

FASEB applauds the Administration's efforts to reduce regulatory burden and we have provided comments to the National Science and Technology Council's Circular A-21 Task Force. In our statement, we proposed the following changes to the policies regulating federally-funded research:

- Eliminate effort reporting
- Minimize financial reporting requirements
- Streamline research training requirements
- Harmonize human subjects protections regulations by
    - Exempting research from the HIPAA Privacy Rule
    - Streamlining regulations and clarifying responsibilities of federal agencies and institutions
    - Holding IRBs, not institutions, accountable for regulatory compliance
- Improve regulation of laboratory animal care and use by
    - Clarifying responsibilities of federal agencies and institutions
    - Reducing the frequency of protocol review
    - Establishing an advisory committee on animal care and use
- Streamline the systems for control of hazardous agents by

    - Stratifying the select agent list[1]
    - Eliminating requirements to quantify biological agents present in a research setting
    - Harmonizing laboratory inspections by multiple agencies of jurisdiction
    - With regard to hazardous chemicals, establish separate policies and procedures for universities so that they are not using the same standards as large manufacturers
- Facilitate reporting of potential conflicts of interest
    - Develop and make available to all investigators a simple, electronic, universal reporting form to help to ensure compliance with reporting requirements while minimizing regulatory burden.

In addition to providing specific recommendations as to how the A-21 circular and related regulatory policies could be improved, we urged the Office of Management and Budget (OMB) to adopt the following guiding principles for reducing cost and burden associated with research:

- Establish mechanisms to evaluate the need for both proposed and existing regulations.
- Assess the impact that the implementation of those regulations has, or is expected to have, on the research enterprise.
- Make every effort to harmonize regulations and guidance among federal agencies.
- Develop regulations that are tiered to the level of risk presented by the situation they are intended to address.

(15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

It would be extremely beneficial for the federal government to help streamline, rationalize, and harmonize the regulations governing human subjects research. We recognize the profound importance of protecting human research participants and support efforts to strengthen those protections. The review process, however, is not calibrated to the risks of research, regulations have not kept pace with changes in the way that clinical research studies are conducted, and regulations and guidance documents are not harmonized across or within agencies. In addition, institutions and institutional review boards (IRBs) impose additional requirements beyond those that are specified in federal regulations or guidance. These are often intended to minimize the risk of liability, but they add little to the protection of participants. Taken together, these factors create unnecessary research delays, confusion, and administrative burden for investigators and, in some cases, work against the goal of protecting participants.

Recently, the Department of Health and Human Services (HHS) issued an Advance Notice of Proposed Rule Making (ANPRM), "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators." In FASEB's response to the Department, we noted that many of the changes proposed in the ANPRM would help to address some of the community's concerns, but suggested that additional changes in policy and practice are needed as well. For example, FASEB suggested exempting research from the HIPAA Privacy Rule, treating all data as potentially identifiable and strengthening standards for protecting those data, issuing guidance encouraging institutions to limit the length and complexity of consent forms and discouraging them from imposing requirements not specified in the regulations.

In conclusion, we express our strong support for the efforts of the Administration and OSTP to promote research and development in biology and recognize their strong commitment to building a better future through research. Harnessing biological research will enable us to meet the health, energy, environmental, and security challenges of the 21st century. To those ends, we hope that the National Bioeconomy Blueprint will focus federal priorities on investigator-initiated basic research, support the efforts of basic scientists who take a more

[1] We are pleased to note progress on this topic.

active role in the downstream development of their work, eschew strategies that divert funding from competitive research budgets, provide greater flexibility in agency rules for use of SBIR/STTR funding, help graduate programs in the biological sciences provide more opportunities for students to develop a broad range of career relevant skills and experiences, and increase efforts to reduce unnecessary regulatory burdens that decrease the productivity of researchers.

We look forward to working with you on these and other initiatives.

Sincerely,

Joseph C. LaManna, PhD

FASEB President

RFI: Building A 21st Century Bioeconomy
Sun 12/4/2011 1:19 PM

Dear White House Office of Science and Technology Policy,

In response to the request for information regarding the 21st century bioeconomy, I offer the following comments relative to question #10:

(10) What roles should community colleges play in training the bioeconomy workforce of the future?

The role of community colleges is emerging as the preferred mechanism for workforce development and initial access to higher education. The 2-year environment offers numerous advantages which uniquely meet the requirements for the bioeconomy of the future; namely, *Relevant Knowledge Now*. A 2-year college setting, or more specifically the technical college setting, has as its mandate to teach the skills necessary to enter the workforce. We therefore offer more than a series of courses designed to deliver course-specific content. Instead, we deliver a program designed to prepare its participants to enter the workforce. The coursework in a program is secondary to the program's collective goal of putting people to work. Program instructors serve as industry advisors grooming participants to become employable.

Numerous surveys identify a bioeconomic industry focus on soft-skills. This serves as a good example of the integrated approach already occurring in the 2-year college setting. We incorporate work ethics, contextual learning, industry-specific curricula and learning communities amalgamated into a college experience designed to deliver a well-trained workforce directly to the industry. This is accomplished for dramatically less cost when compared with other institutions of higher learning. The 2-year college is nimble, effective and measured by the number of students entering the workforce. I challenge the White House Office of Science and Technology Policy to find a more effective and well-suited venue for the preparation of tomorrow's bioeconomy workforce.

Thank you for this opportunity to offer information to our country's leadership. If ever we needed effective leadership, it would be now.

Philip Gibson, Ph.D.
Bioscience Program Director
Gwinnett Technical College
[redacted]
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THE AMERICAN SOCIETY FOR CELL BIOLOGY

Request for Information: Building A 21st Century Bioeconomy
Reply by The American Society for Cell Biology

1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

One of the biggest challenges to the health sciences will be maintaining a long-term vision of impact of the biological research on human health. Leveraging the tremendous advances in biology has already led to remarkable progress in diagnosis. However, the translation from a diagnostic phase to a successful treatment will be slower. It is important that the government stay the course to realize the gains of biomedical research.

With the costs of health care skyrocketing, a challenge to the biomedical research community is how we can make an impact on stabilizing these costs and avoiding the 'valley of death' that comes between progress in research and diagnosis, and subsequent translation of these findings to successful treatments.

One of the greatest challenges facing the American bioeconomy and general economy is research into the diseases of the brain. Three examples are: 1) The health care and emotional impact of diseases such as Alzheimer's disease in older people when they would otherwise be functional; 2) The impact of traumatic brain injury on soldiers returning from war and the increased susceptibility of these soldiers to Alzheimer's disease because of traumatic brain injury; 3) The psychiatric consequences of war oneven physically healthy soldiers. Collectively these problems have trillions of dollars of healthcare and economic impact while the Federal government barely invests $1-2 billion a year to fight them. We are still farther than we want to be from solutions. But an increased effort to understand how all cells function, to understand how basic cellular functions are used in neurons, and to understand how these functions fail in all of these disease conditions (and many others) is essential.

2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

The foundation for the bioeconomy will depend upon sustainable, dependable growth

in biomedical research. The last decade has seen boom and bust funding cycles that have led to irresponsible growth in infrastructure followed by underfunding of the science and technological technologies, ultimately undermining the investment in infrastructure.

The federal government should immediately double its portfolio of basic research ranging from basic cell biology to neural network formation and function in brain biology and disease. It should then commit to inflation +2% growth in the coming years for funding of this vital research until the problems are solved.

3) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative1)?

High throughput technology generates massive amounts of data. However, the usefulness of this data is extremely dependent upon validation of its accuracy and validity. We are overrun with data at the moment, and it's been very difficult to sort out what it all means. Better statistical and combinatorial approaches are necessary to help find meaning and identify the rare mutations etc within all the noise of the datasets.

Reducing sequencing costs to the amounts similar to the cost to sequence the human genome will have tremendous impact directly on human research. This reduction in cost per base pair would also revolutionize the utility of model systems from which we derive most of our molecular knowledge of human. The ability to change as well as to assess DNA sequence would also revolutionize biology. With this in mind, the development of technology to allow high throughput DNA assembly of Kbs of DNA (currently 100 bps) should be emphasized.

Federal priorities should also focus on encouraging teams of interdisciplinary investigators to work together on important problems. While it is imperative to maintain investigator initiated projects, incentivizing collaborative interdisciplinary research will yield the greatest impact in the coming years scientifically and economically.

4) The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

Investigator initiated research is probably the most important because each problem will actually be different and requires focus and insight to solve. Critical technical

challenges are quality control and curation of large high throughput data sets.

Almost all our knowledge of human gene function has come from basic research analyzing orthologs of human genes in model systems. These model systems have tremendous experimental advantages both technically and ethically. Indeed the function of the 70% will undoubtedly only be discovered through model systems. Government should spend a significant portion of its budget on basic research of human orthologs in existing model systems and in the development of new model systems.

5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

More interactions and successful collaborations are necessary to help bridge the divide between the lab and the marketplace. There is a difference in the mindsets of the academic world verses companies, as the goals are often very different. Companies won't put efforts into drug discovery until the knowledge of potential drug targets is already quite far along and developed. In addition, the academic community often thinks its job is done once a potential target is identified.

An enormous barrier is a very complicated landscape of material exchange. Material Transfer Agreements (MTAs) complicate every academic and scientific transaction, even those essential to reproduce results to find out if they are true. One recommendation would be to put statutory limits in all MTAs so that they do not outlive patents. The other issue is how to deal with risk. On the one hand, the American people want new therapies as rapidly as possible. On the other hand, they want zero risk. Legal protection for good faith and honest problems with marketed therapies would be a good first step. Getting consumers to realize that there is no substitute for their own education and ensuring availability of accurate information for all medical consumers is a good second step. Finally, all information in an Investigational New Drug (IND) Application and subsequent filings with the Food and Drug Administration (FDA) prior to and post-registration should be publicly available so that any patient can consult their physician or other experts to evaluate for themselves what the risk-benefit trade-offs might be.

9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Graduate programs need to be more open about all the different career opportunities that exist for PhDs in the biomedical community. A PhD in science is great training for so many careers (from patent law, to investment banking, to writing and publishing, to academic research administration, to big pharma, and small biotech startup, etc). Often, it is only when students are in their last year or two that they start to think about employment possibilities outside of academia.

For that reason, first hand exposure to, and experience working in, the private sector will be an essential addition to doctoral training. Priorities differ considerably between academic research labs and the private sector, so it is important for a PhD student to demonstrate that he/she has a solid understanding of what the private sector values and how projects are designed around achieving their goals. Funding for internships will be extremely important for supporting this.

In addition, more informational seminars and career panels should take place through the graduate student's education, and could even be incorporated into the yearly graduate program retreats. Perhaps even non-academic PhDs could be placed on graduate students admission committees, or even thesis committees as external advisors.

11) What role should the private sector play in training future bioeconomy scientists and engineers?

The private sector should provide paid internships. These are currently much more common in engineering than in the basic sciences, but needs to expand to include all fields of biomedicine.

12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

For graduate students, finding a suitable academic postdoc is often much easier than finding an industrial postdoc, because it is very difficult for many PhDstudents to make contacts in industry. While on-campus visits by academic researchers are commonplace (departmental seminars, workshops, sabbatical leave, etc.), access to working professionals is often limited to large national meetings. Thus, recruiting PhDstudents to complete industry internships will be a major improvement.

17) What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

Public-private partnerships that bring multiple companies and federal investment together to solve major pre-competitive problems such as better toxicology predictions, stem cell models of disease, and shared technical resources could limit duplication and maximize synergy.

Response to Request for Information Regarding a National Bioeconomy Blueprint
University of Houston
December 2011

This document is submitted in response to the White House Office of Science and Technology Policy's (OSTP) request for information to inform the upcoming National Bioeconomy Blueprint. Located in the country's fourth-largest city, the University of Houston (UH) is a thriving Tier-One research institution pursuing innovative discoveries in the biological sciences. What's more, UH is one of the nation's most diverse research institutions, having recently been designated as a Hispanic Serving Institution by the Department of Education. Enrolling over 39,000 students, UH is also the second largest institution of higher education in the state of Texas and a driving force behind the greater Houston area's thriving life sciences industry.

Research is not only an element of the nation's bioeconomy, but is the foundation on which our biological sciences industries are built. None of the technologies which support countless jobs across the energy, agricultural, and health sectors would be possible without the early-stage basic and applied research carried out at institutions like UH. With this in mind, it is critical that the Blueprint include research as a fundamental piece of a strong bioeconomy. Further, UH encourages OSTP to include in the Bioeconomy Blueprint its support for a robust federal biological research enterprise to catalyze future advances that will ensure our global competitiveness. Sustained federal support for biological research will drive solutions to national issues in energy, health, and national security while at the same time supporting thousands of new jobs. For example, at UH, faculty Jeffrey Rimer and Peter Vekilov have recently received a grant from the Department of Defense to develop a completely new method to develop anti-malarial drugs.

In addition to basic research activities, it is important for federal biological research initiatives to be interdisciplinary, as many game-changing advances lie at the nexus of biology and other fields. For example, the UH Department of Electrical and Computer Engineering is working with medical researchers to develop software that can quickly recognize tissue images to help diagnose and treat disease. Projects like these illustrate that creative interdisciplinary approaches are necessary to leverage all available resources and expertise in support of the nation's bioeconomy. This includes adopting complementary approaches at the federal level which bring together multiple agencies working towards innovative solutions in the biological sciences.

Finally, implicit in this effort is the need to ensure support for high-risk, high-reward projects despite overall budget constraints. Pursuing potentially disruptive discoveries requires that federal agencies support projects which carry greater risk, but also offer the potential to transform an industry or overcome a challenge if successful. Projects such as those supported by the Advanced Research Projects Agency-Energy (ARPA-E) hold the ability to stimulate quantum leaps towards overcoming national concerns. At UH, the Center for Nuclear Receptors and Cell Signaling is using the basic science of cell biology to find ways to treat diseases such as cancer, Alzheimer', and Multiple Sclerosis.

Beyond research, it is important that the Bioeconomy Blueprint include measures to speed the transfer of innovative discoveries from the laboratory to the commercial marketplace. Effective technology transfer policies are essential to helping the nation's research universities contribute to the strengthening of the bioeconomy through the creation of new companies and partnerships which drive economic growth. UH is aggressively moving forward in the technology transfer arena, and these efforts

are directly enhancing the already burgeoning energy and life sciences industries in the greater Houston area.

UH is investing in a Center for Industrial Partnerships to transfer technology to the bioeconomy. This Center is helping to overcome barriers to the successful transition of new technologies from the research laboratory to the commercial marketplace. In addition, federal policies such as increased proof of concept funding to bridge the "valley of death" and encourage investors to be more active in smaller markets will more fully leverage university resources in support of the bioeconomy.

As one of the country's most diverse research institutions, UH is playing an important role in preparing the next generation workforce to participate in the bioeconomy. UH strives to foster skills in its students at both the undergraduate and graduate levels which will translate directly to fields including energy and the health sciences. Specifically, UH trains its graduates to work on diverse teams that contain the range of expertise necessary to solve the country's most urgent challenges. Scientists and engineers in both academia and industry will need appropriate awareness of the interdisciplinary research questions central to the bioeconomy. It will be critical to train biological scientists with highly developed quantitative skills as well as physical scientists and engineers with appropriate awareness of challenges in the life sciences.

In addition, UH believes that federal programs should support university efforts to develop curricula and programs focused on horizontal integration of training across disciplines while maintaining appropriate in-depth training in students' core research areas. For example, Dr. Rupa Iyer of the UH College of Technology has recently received an NSF grant titled "From Nature to Lab to Production-Infusing Cutting Edge Technology into Undergraduate Biotechnology Curriculum."

UH is also committed to utilizing its extensive relationships with the private sector in support of developing a top-quality workforce for the bioeconomy. The UH System produced 3500 health and biology related degrees in 2010 in areas such as nursing, biology and biochemistry, pharmacy, and lab technicians that will support local industries. Effective federal policies such as promoting fellowships that allow students to spend part of their graduate careers working in industry or other sectors help create networks between academia and industry, foster real-world learning, and provide students with greater understanding of workforce opportunities beyond the lab. Supplements to research grants for appropriate commercialization activities can also be important in developing the workforce which is the lifeblood of industries grounded in the biological sciences.

Institutions like UH are important actors in the expansion of the nation's bioeconomy. Our research, technology transfer, and workforce training initiatives contribute to all levels of the bioeconomy and our partnerships with industry spur economic development in our home region. UH appreciates the opportunity to comment on this important topic.

Mon 12/5/2011 12:09 AM
response to Fed Reg notice 62870

Hello,
I am writing to respond to the Request for Information: Building a 21st Century Bioeconomy which appeared in the Federal Register Oct 11, 2011.

Question 5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets?

There are several causes. One part is due to the lack of training scientists receive in how to commercialize their technology. A second is a lack of funding for the development steps necessary. NIH, NSF, EPA, etc. typically fund research; they do not support development in the same way that a large firm would have separate R&D divisions. In order for more technologies developed in U.S. labs to lead to products there needs to be a fundamental shift in how we fund science and technology so as to raise the profile and financial support for development. This could be achieved by requiring that some proportion of federally funded projects have a path by which the work could lead to commercialization (and have private sector partners). Several agencies took a similar step recently with requirements to include non-federal matching funds for any research project. This does not accomplish the task of furthering development. If the federal science and technology priorities are research, that is what we will have. If the priorities are research and development (and supported in that way), then both will be facilitated by the science community. An important additional factor includes the challenging regulatory steps (and difficulty gaining funding to permit that they be addressed).

Question 6) What changes to SBIR / STTR programs are needed?

These programs are essential for fostering development, but they need to be better connected to the foundational research supported by the agencies. There currently is no direct connection between traditionally supported research and the types of development done in SBIR / STTR programs. An IP bridge needs to be constructed. Also, some firms use SBIR / STTR programs as a frequent stream of support but do not translate many of these projects into products. A comprehensive review of such track record needs to be a part of the proposal review.

Question 9) What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

A substantial percentage of graduate students (seeking M.S. and Ph.D. degrees) are not U.S. citizens and are supported by research grants predominantly from federal sources. Many graduate programs do this because there is a lack in the number of U.S. citizens that receive B.S. degrees who desire to continue for an advanced degree since good, high-paying jobs can be had, especially in engineering, with only the B.S. degree. This process inevitably results in federal funds supporting the training of students who then return to their home country due to the large difficulties in obtaining a U.S. work visa after their studies are complete. A change in policy is needed such that any student receiving an advanced degree in an area of technical need (science or engineering or similar) should receive along with their diploma an expedited process for obtaining citizenship. The current process is in effect a brain drain on U.S. resources.

A further step is to support K-12 education on the translation of technologies. Schools focus on the discovery part of science, but very little on the conversion to products. We need to lay the groundwork in science education that science's goal is not just to gain knowledge, but to make improvements in the lives of people. Higher education programs are quite willing to work with K12 (as evidenced by the GK-12 (graduate K-12) programs supported by NSF). These activities need to be expanded.

Mark Riley, Ph.D.
Professor and Department Head
Ag. and Biosystems Engineering
The University of Arizona

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

Request for Information: Building A 21st Century Bioeconomy

Questions No 1, 8, 9 and 10:

1) One grand challenge to creating a thriving bioeconomy is to make community college systems the foundation of biotechnology workforce training. Four-year colleges and universities graduate potential management personnel, but a greater and unmet need is for people to do the actual hands-on laboratory work needed for research and development as well as production. These laboratory skills can and are being taught by community colleges. The first challenge is to put the full force of White House public relations and policy-making behind biotechnology education in community colleges.

Such a program is well established at City College of San Francisco where the BioLink National Center was founded 13 years ago and thrives today. (Please see submission to this RFI by Ms. Elaine A. Johnson PhD, Executive Director) These graduates work in all areas of life sciences research. Many California taxpayers and observers of higher education's ongoing pleas for increased funding have come to question whether the four-year colleges are meeting the needs of today's economy. They see a mismatch between higher education and the economy's workforce needs. The "biotech age" needs people with high end skills that increasingly do not come with a bachelors degree. A technically-skilled 21st century American bioeconomy workforce requires commitment to and investment in education and training. The bulk of the training can and should be in the community colleges.

Thank you for the opportunity to comment on this important subject.

Barbara W.Wanvig
San Francisco, CA

Federation of Animal Science Societies

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December 6, 2011

Office of Science and Technology Policy
Executive Office of the President
725 17th Street Room 5228
Washington, DC 20502
bioeconomy@ostp.gov

RE: Request for Information: Building A 21st Century Bioeconomy

To Whom It May Concern:

I am writing on behalf of the Federation of Animal Science Societies (FASS) in response to the notice placed in the Federal Register on October 11, 2011 requesting information on "Building A 21st Century Bioeconomy". FASS represents over 10,000 scientists and has great interest in advancing biological research innovations to meet the national challenges identified in the request for information, including health, food, energy, and the environment. We appreciate the opportunity to comment and wish to highlight a number of high priority policy issues related to the animal sciences.

Attached to this letter is a series of Science Policy Statements that FASS has developed over the last two years. The topics covered by these policy statements include many of the issues raised in the Request for Information, including nutrition and health, food security, and environmental stewardship. We believe that these policy statements can be helpful to the Office of Science and Technology Policy as its leaders continue to develop the National Bioeconomy Blueprint. Additional information regarding these issues, including recent FASS-sponsored webinars, can be found at the FASS website: www.fass.org.

Please let us know if you have any questions regarding the attached policy statements or if FASS can be of further assistance. Lowell Randel serves as the FASS Science Policy Director, and he can be reached at [redacted]. FASS and its network of scientists stand ready to help in building our nation's bioeconomy.

Sincerely,

James W. Oltjen

James W. Oltjen, Ph.D.
President, Federation of Animal Science Societies

BIOTECHNOLOGY AS A TOOL TO ENHANCE SUSTAINABILITY FOR ANIMAL PRODUCTION

Rationale:

The United Nations Convention on Biological Diversity describes Biotechnology as "Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use" (1). This definition extends to many aspects of animal agriculture used over the last century including animal breeding, artificial insemination, and the use of vaccines. More recently, biotechnologies are used for gene transfer to modify gene expression (transgenics), in health care (insulin for diabetics), or for environmental clean up (bacteria that can digest oil). In addition, comparing genomics of organisms that are resistant and susceptible to disease to identify genetic markers is used to select for genotypes that favor desired health status or production traits.

The world population will increase from 6.7 billion to 9.2 billion by 2050 (2,3). By 2020, the global demand for meat will increase by 58%; milk consumption will increase from 568 to 700 million tons; egg production will increase by 30%; and demand for poultry, beef and pig meats will increase by 85%, 80%, and 45%, respectively, from 1995 levels (2). With only 2% more arable land available for food production in North America in 2050, there must be continual improvement in productivity per unit of land area (3). FAO estimates that 70% of these gains in production must come from the use of new technologies (4). Modern biotechnology offers solutions to challenges for environmentally sustainable animal production that are not achievable using historical technologies. However, the use of biotechnology in food animal production can be a contentious issue for some consumers.

Policy Statement:

FASS recommends that the basis for acceptance of the use of biotechnology to improve the sustainability of agricultural production be from a science-based viewpoint. FASS believes that adoption of modern biotechnology is critical to meet the growing demands for sustainable food production in the next 25-50 years. FASS believes that consumers should have the right to choose what technology they embrace by having the freedom in the marketplace to buy products with the attributes they desire.

Policy Objectives:

- FASS endorses the importance of continuing to do research and where applicable adopt modern biotechnologies to safely improve the attributes of agricultural production systems, and the plants and animal products used and consumed by the world's human population.
- FASS endorses that rational, scientifically-based systems be adopted in governmental policy regarding the research and introduction of agricultural biotechnologies, including the production, marketing, and global trade of plant and animal products derived from the use of biotechnology.
- FASS can provide information and educational assistance to any agency or educator as a resource to support the science underpinning the use of a biotechnology related to animal agriculture.
- FASS encourages funding for research and education necessary to provide the fundamental biological knowledge of organisms, including genomes, that will lead to strategies for global solutions that address the grand challenges for production of abundant, safe and affordable foods for the 21st century and beyond.

References:

1. "The Convention on Biological Diversity (Article 2. Use of Terms)." United Nations. 1992. Retrieved on February 6, 2008.
2. http://www.grid.unep.ch/geo1/ch/ch4_9.htm Accessed 07DEC2010.
3. USDA Agricultural Projections to 2017. Office of the Chief Economist, World Agricultural Outlook Board, U.S. Department of Agriculture. Prepared by the Interagency Agricultural Projections Committee. Long-term Projections Report OCE-2008-1, 104 pp.
4. Food and Agriculture Organization of the United Nations (FAO). 2004. Protein Sources for the Animal Feed Industry. Expert consultation and workshop. Bangkok 29April-3May 2002. FAO, Rome.

Adopted by the FASS Board of Directors on May 5, 2011

For more information, please contact FASSPolicyStatements@assochq.org

CO-PROMOTION OF ENVIRONMENTAL STEWARDSHIP AND PRODUCTION EFFICIENCY

Rationale:

Preservation of the ability of future generations to meet their needs while adequately serving the present population (sustainability) requires control of greenhouse gas (GHG) production and avoiding damage to air, water and soil. Simultaneously, growing populations and rising purchasing power in developing countries will strain the earth's finite capacity to produce enough high-quality protein and nutritionally rich foods, demanding efficient production of food. Fortunately, a growing body of evidence related to production of foods of animal origin suggests that production efficiency leads to environmental stewardship.

The current situation is:

- The United Nations (UN) estimates the current world population to be about 6.9 billion and projects it to rise to more than 9 billion in 2050. (1)
- Population growth rates in developing countries remain nearly twice those of developed countries. These rapidly increasing populations are accompanied by increased income and increased demand for meat and other animal products (50% increase by 2020). (2)
- Food security is and will continue to be a major challenge, (3, 4) A recent report by the UN's Food and Agriculture Organization (FAO) estimates that global food production must increase 70% by 2050. (5) Even within the US, USDA estimated that in 2008 14.6% of households were food insecure during at least some portion of the year. (6)
- Properly managed modern animal production systems and technologies have clear environmental advantages over older, less efficient production models. To produce the same amount of milk, modern dairy production practices require 79% fewer animals, 77% less feed, 65% less water, and 90% less land than systems used in 1944. Modern dairy systems produce 76% less manure and 63% less carbon than those of the 1940s. (3)
- Contrary to some previous reports, a recent study found that the contribution of direct livestock emissions (from enteric fermentation and manure) amounts to less than 3% of total GHG emissions caused by man. (7)
- The FAO concluded that intensification of livestock production offers significant opportunities to mitigate climate change, largely by increasing efficiency of feed use and thereby reducing the need to expand feed production onto environmentally critical land. (8)

Policy Statement:

FASS supports minimization of greenhouse gas production and proper management of manure nutrients to avoid environmental damage from the necessary production of food of animal origin.

Policy Objectives:

- FASS opposes restriction on animal production technology when these restrictions may reduce efficiency and therefore increase environmental degradation.
- FASS supports increased funding for research, extension and education directed to improving environmental quality by increasing the efficiency of feed use by animals.

References:

1. World Population Prospects: The 2008 Revision Population Database. United Nations Population Division. http://esa.un.org/unpp/
2. USDA Agricultural Projections to 2017. February 2008. USDA Economic Research Service.
3. Capper et al. The environmental impact of dairy production: 1944 compared with 2007. Journal of Animal Science 2009. 87:2160-2167.
4. http://www.beeftechnologies.com/environImpact/impact-resources-land.html
5. How to feed the world in 2050. A report from the World Summit on Food Security held in Rome, November 16-18, 2009
6. Household Food Security in the United States, 2008. November 2008. USDA Economic Research Service.
7. Pitesky et al Clearing the Air: Livestock's Contribution to Climate Change. In: Advances in Agronomy, Vol. 103.
8. Livestock's Long Shadow – Environmental Issues and Options. Food and Agriculture Organization of the United Nations. Rome, 2006.

Adopted by the FASS Board of Directors on March 29, 2010

For more information, please contact FASSPolicyStatements@assochq.org

FARM ANIMAL WELL-BEING

Rationale:

Scientists and animal producers have an ethical obligation to provide environments for farm animals that promote animal well-being. Determination of the animal's well-being is only gained through understanding the science of farm animal needs. The production of safe and high-quality animal-based food and fiber in a sustainable manner is essential for consumers as well as livestock and poultry producers. It is in the interest of animal industries and research and teaching organizations to use science-based standards to provide the best possible animal care.

- Animal scientists have conducted scientific investigations that establish and refine management practices that provide for optimal care, handling, housing, nutrition, and husbandry practices for farm animals.
- FASS has published a compilation of the scientific literature directed at sound farm animal care at universities, government laboratories, and research companies in its Guide for the Care and Use of Agricultural Animals in Teaching and Research, the Ag Guide. The Ag Guide provides up-to-date information on science-based farm animal care in agricultural and biomedical teaching and research1. Although other guides are available, the Ag Guide is the most comprehensive, current, science-based document authored by dozens of professional animal scientists and peer reviewed by individuals and organizations.
- FASS encourages those involved in commercial animal agriculture and oversight of teaching and research programs to use science-based criteria to develop and refine guidelines for farm animal care.
- Companies in the food marketing chain are encouraged to support science-based animal care standards as they implement animal care programs.
- Animal scientists are investigating current and new production systems to promote sound farm animal care. Changes in farm animal care practices need to be considered in the context of impacts on the environment, food safety, and societal views. Understanding and considering societal concerns will lead to more sustainable production systems.

Continued improvement in husbandry practices enhances the well-being of animals and is a necessary part of satisfying the increasing world demand for animal-based food and fiber. The public has a legitimate interest in the potential environmental, food safety, and animal welfare implications of livestock and poultry production. The animal science community must faithfully, and in an unbiased manner, examine those implications in a scientifically rigorous fashion—investigating, teaching, and implementing those practices and technologies found to maximize production efficiency while providing for the well-being of the animal.

Policy Statement:

The Federation of Animal Science Societies (FASS) encourages the use of management practices and technologies that have been developed through scientific investigations and have been shown to promote animal well-being.

Policy Objectives:

- Support the use of science-based practices such as described in the Guide for the Care and Use of Agricultural Animals in Research and Teaching (1) and/or other science based appropriate standards that promote animal-well being in farm animals in all settings.
- Support the use of science-based practices that promote animal-well being in laboratory animals in research settings.
- Support the use of harmonized guidelines for farm animal care at universities, government laboratories, and industry research facilities.

References:

1. FASS. 2010. Guide for the Care and Use of Agricultural Animals in Teaching and Research. 3rd ed. Federation of Animal Science Societies, Champaign, IL. Available online: http://www.fass.org/page.asp?pageID=216**.**

Adopted by the FASS Board of Directors on August 12, 2010

For more information, please contact FASSPolicyStatements@assochq.org

ENSURING FOOD SECURITY THROUGH RESEARCH, EXTENSION AND EDUCATION

Rationale:

The high food prices and food shortages that occurred in several countries during 2008 provide a sharp reminder of the fragility of the food security of the United States and the world. Our food production system has been remarkably successful in meeting food needs in the past, but the challenge continues. Food demand continues to grow rapidly, making it imperative that we substantially increase public funding for improvements in food production.

The current situation is:

- The world's human population continues to grow, and large numbers of people in developing countries are emerging from deep poverty and demanding improved diets; these factors will challenge the world's food production capacity during coming decades.
- To feed the people of the world sustainably, food producers must continue to increase the efficiency with which they use the earth's limited resources. That includes continued increases in efficiency of livestock production.
- Food reserves have dwindled during recent years; for example, the soybeans remaining at the end of the 2008-2009 crop year are projected to be only about 2 weeks' supply (1).
- Large amounts of crops are now being diverted from the food chain to produce biofuels.
- Due to the historically productive research, extension and education infrastructure, the U.S. enjoys the safest and most abundant supply of food in the world, contributing to public health.
- Legitimate societal interest in animal well-being, food safety, food composition and environmental quality expands the scope of research needed.
- State funding for agricultural research has dropped substantially during recent decades, and research funding from USDA has not made up the loss (2); the costs of research addressing issues of societal concern compete for already strained budgets for research on production efficiency, which is critical to sustainable production. At the same time, much research funding has been diverted from food production to biofuels production.
- Funding for research in livestock production is now especially important because of the increased consumption of animal products by people in developing countries, but such funding continues to lag behind the needs.

Policy Statement:

The Federation of Animal Science Societies (FASS) supports increased funding for research, extension and education related to food production in order to strengthen the food security of the United States and the world.

Policy Objectives:

- FASS supports increased funding within the USDA National Institute of Food and Agriculture for the basic and applied research on food production necessary to sustainably meet the food needs of the world's population.
- FASS supports increased funding for research on production of foods of animal origin, including research on production efficiency, animal well-being, food safety, food composition and environmental quality.

References:

1. World Agricultural Supply and Demand Estimates. ISSN: 1554- 9089. U.S. Dept. of Agriculture, Econ. Res. Serv. June 10, 2009.
2. Schimmelpfennig, David, and Paul Heisey. U.S. Public Agricultural Research: Changes in Funding Sources and Shifts in Emphasis, 1980- 2005. EIB- 45, U.S. Dept. of Agriculture, Econ. Res. Serv. March 2009.

Adopted by the FASS Board of Directors on October 23, 2009

For more information, please contact FASSPolicyStatements@assochq.org

INTERNATIONAL AGRICULTURAL DEVELOPMENT AND THE ROLE OF ANIMALS

Rationale:

About a billion people in the world are food-insecure (1), unable to obtain enough food every day, creating a serious humanitarian and national security problem. The solution for this enormous and complex problem must include increased food production both globally and in the countries with greatest food insecurity.

Important aspects of the issue include:

- Global food security is impossible without global food sufficiency.
- With increasing populations and purchasing power in developing countries, demand for animal products will increase dramatically during coming decades.
- Crop yields and animal efficiency are substantially lower in developing countries than in developed ones, providing opportunity for rapid improvement.
- Past success shows that necessary increases in food production require significant public investments in research, extension and education.
- Public research and educational funding directed to food production has diminished during recent decades (2).
- Agricultural development involves not only farming technology, but also infrastructure such as roads, supply and marketing chains, banking, legal systems and others.
- Livestock benefit smallholders in resource-poor regions by utilizing non-food biomass, as a source of essential nutrients and as a cash reserve

Policy Statement:

The Federation of Animal Science Societies (FASS) strongly supports all efforts to enhance international agricultural development to promote global food security, and emphasizes that animal production must be an integral component of developing agricultural systems.

Policy Objectives:

- Promote awareness of the food situation in developing countries among the U.S. population to build support for international agricultural development.
- Provide targeted development programs and locally-relevant research, extension and education to support food systems, including livestock production.
- Address the impacts of climate change on agriculture, including livestock production, and the environmental sustainability of food production systems.
- Increase the supply of animal products to improve the nutritional status and health of people in the developing world.

References:

1. FAO, 2009. ftp://ftp.fao.org/docrep/fao/012/i0876e/i0876e.pdf. Accessed February 22, 2011.
2. Eicher, 2009. Rev. B us. Econ. LIV.3:238-257.

Adopted by the FASS Board of Directors on May 5, 2011

For more information, please contact FASSPolicyStatements@assochq.org

NUTRITION AND HEALTH PROVIDED BY ANIMAL PRODUCTS

Rationale:

A diversity of food sources remains a key element to a balanced diet, good health and even survival (1). Animal products are excellent sources of high quality protein and other nutrients that are readily absorbable, and thus make important contributions to a nutritionally balanced diet.

As societies develop economically, they tend to add diversity to their diets. Typically, animal products are more expensive than vegetable products but animal products are well recognized for bringing a more balanced nutritional status to a population. Diets that exclude animal products often require dietary supplements (2,3). Furthermore, meat, eggs and dairy foods provide complementary nutrition to most indigenous diets, resulting in improved nutritional status and health of global populations.

Policy Statement:

FASS works to raise the nutritional status of the global population by expanding the diversity of foods available to all, especially through the inclusion of nutritionally dense animal products.

Policy Objectives:

- FASS supports having available to all people all the foods necessary for a balanced diet and optimal nutritional status. Nutrient density represents a major factor that is efficiently delivered through dairy, meat and egg products.
- FASS can provide nutritional data and educational assistance to any agency or educator showing how to optimize local diets in order to achieve higher nutritional status in a given population.
- FASS remains committed to developing new technology that will enhance sustainability while decreasing the cost of production of animal products and thus the cost to consumers.
- FASS encourages funding for research and education to meet these three objectives that focus on improving the nutritional status of all people.

References:

1. Arimond, M. and M.T. Ruel. 2004. Dietary diversity is associated with child nutritional status: Evidence from 11 demographic and health surveys. J. Nutr. 134:2579-2585.
2. Shils, M.E., M. Shike, A.C. Ross, B. Caballero, and R.J. Cousins. 2005. Modern nutrition in health and Disease. Lippincott, Williams, and Wilkins.
3. **Elmadfa, I. and I. Singer. 2009. Vitamin B-12 and homocysteine status among vegetarians: a global perspective. Am.J. Clin. Nutr. 89(suppl):1693S-1698S**

Adopted by the FASS Board of Directors on August 12, 2010

For more information, please contact FASSPolicyStatements@assochq.org

PRESERVING THE BENEFITS OF ANTIBIOTICS FOR PEOPLE AND ANIMALS

Rationale:

Antibiotic resistance in pathogens occurs too often and with increasing frequency, interfering with treatment of sick people and animals. Although antibiotics and antibiotic resistance are natural phenomena, the population of resistant bacteria is increased by introduction of antibiotics into an environment. Therefore, it is important to examine carefully the wisdom of all uses of antibiotics, in both humans and animals.

Key considerations regarding the use of antibiotics in food animals include:

- Antibiotics are used in the care of food animals for disease treatment, disease prevention and increased production from limited feed resources.
- Feeding antibiotics to young animals is particularly effective in decreasing mortality and morbidity and thereby increasing animal welfare.
- In practice (1), targeted restrictions on antibiotic use have resulted in less total antibiotic use than a total blanket ban on continuous feeding of antibiotics.
- Antibiotic use in animals can lead to resistant pathogens in humans, but the extent to which antibiotic use in livestock production contributes to the overall problem is not fully understood.
- Exhaustive reviews (2,3) have not shown clear evidence of a significant contribution.
- Some classes of antibiotics used in food animals are not currently used in human medicine, so elimination of their use would not be expected to affect antibiotic resistance in humans.
- Antibiotic use in food animals is strategically targeted, following judicious use guidelines based on reliable evidence developed by the American Veterinary Medical Association (4) and other organizations.
- To decrease antibiotic use, food animal producers have implemented an impressive array of approaches to keep animals healthy and reduce the need for antibiotics, including all-in/all-out animal flow, rigorous biosecurity measures to keep diseases out of farms, intense sanitation, and vaccines.
- The world must double food production in the next 4 decades with limitations and additional inputs and judicious use of antibiotics can contribute to efficient food production to meet this demand.

Policy Statement:

The Federation of Animal Science Societies (FASS) strongly supports the judicious use of antibiotics in food animal care consistent with the health and welfare of the animals, with preserving the value of antibiotics in protecting human and animal health, and with efficient use of the earth's resources in food production.

Policy Objectives:

- Develop strategically targeted regulations for antibiotic use in food animals that are focused on specific risks, specific classes of antibiotics and specific uses to most effectively protect human and animal health.
- Continue the use of antibiotic in food animal populations where it is demonstrably efficacious in treating disease, promoting health, and increasing global food security.
- Develop regulatory systems that support use of antibiotics for disease prevention where justified.

References:

1. Ministry of Food, Agriculture and Fisheries. 1996-2008. DANMAP 2008: Danish Integrated Antimicrobial Resistance Monitoring and Research Program. http://www.danmap.org/. Retrieved January 18, 2010.
2. National Research Council 1999. The Use of Drugs in Food Animals: Benefits and Risks. National Academy Press.
3. Institute for Food Technologists. 2006. Antimicrobial Resistance: Implications for the Food System. http://www.ift.org/Knowledge%20Center/Read%20IFT%20Publications/Science%20Reports/Expert%20Reports/Antimicrobial%20Resistance.aspx?page=viewall. Retrieved June 10, 2010.
4. American Veterinary Medical Association. 2009. Judicious Use of Antimicrobials. http://www.avma.org/products/scientific/jtua.pdf. Retrieved June 10, 2010.

Adopted by the FASS Board of Directors on August 12, 2010

For more information, please contact FASSPolicyStatements@assochq.org

PRESERVING WATER QUALITY ASSOCIATED WITH LIVESTOCK AND POULTRY PRODUCTION

Rationale:

Livestock and poultry production has evolved to fewer and larger production units for several reasons, including the benefits of scale in efficient use of resources. As livestock and poultry production units have increased in size, there have been concerns about their impact on natural resources including water quality.

- Animal production systems have adopted many technologies designed to protect water quality, guided by a complex set of federal and state regulations. A few examples of those technologies include:
    - Containment of process-generated waste water and storm water runoff
    - Rigorous construction standards for manure storage containers made of earth, concrete or other materials
    - Application of manure to cropland at rates corresponding to the uptake of nutrients by the crops
    - Incorporation of manure into soil when applied to cropland
- Application of these technologies requires a high level of expertise and management.
- Animal producers, their families, their employees and their animals have the same needs for high-quality water as other people.
- Recycling of nutrients in animal manure to cropland is the oldest recycling program, and throughout history has contributed to food security.
- The world must double food production in the next 4 decades with little new land available for cultivation, less water available for irrigation, and perhaps limited supplies of fertilizers. Thus we must maximize food production from the earth's limited resources.

Policy Statement:

FASS supports preservation of water quality along with efficient use of resources in animal production.

Policy Objectives:

- FASS supports scientifically based protection of both ground water and surface water.
- FASS supports policy that acknowledges the value of efficient animal production in promoting food security.
- FASS supports focus on protection of the environment and on efficient use of resources.
- FASS encourages funding for research and education to meet objectives that focus on improving nutrient management and water quality.

Adopted by the FASS Board of Directors on May 5, 2011

For more information, please contact FASSPolicyStatements@assochq.org

National Agricultural Biotechnology Council

B15 Boyce Thompson Institute, Ithaca, NY 14853
607-257-4856 Fax-254-8680 NABC@cornell.edu
http://nabc.cals.cornell.edu

Providing an open forum for exploring issues in agricultural biotechnology

Response to OSTP's

Request for Information: Building a 21st Century Bioeconomy

The National Agricultural Biotechnology Council, a consortium of major public-sector agricultural research institutions, is pleased to provide the following documents—cover pages herewith appended with URLs—that address the grand challenges for the bioeconomy in agriculture, health, energy and climate change:

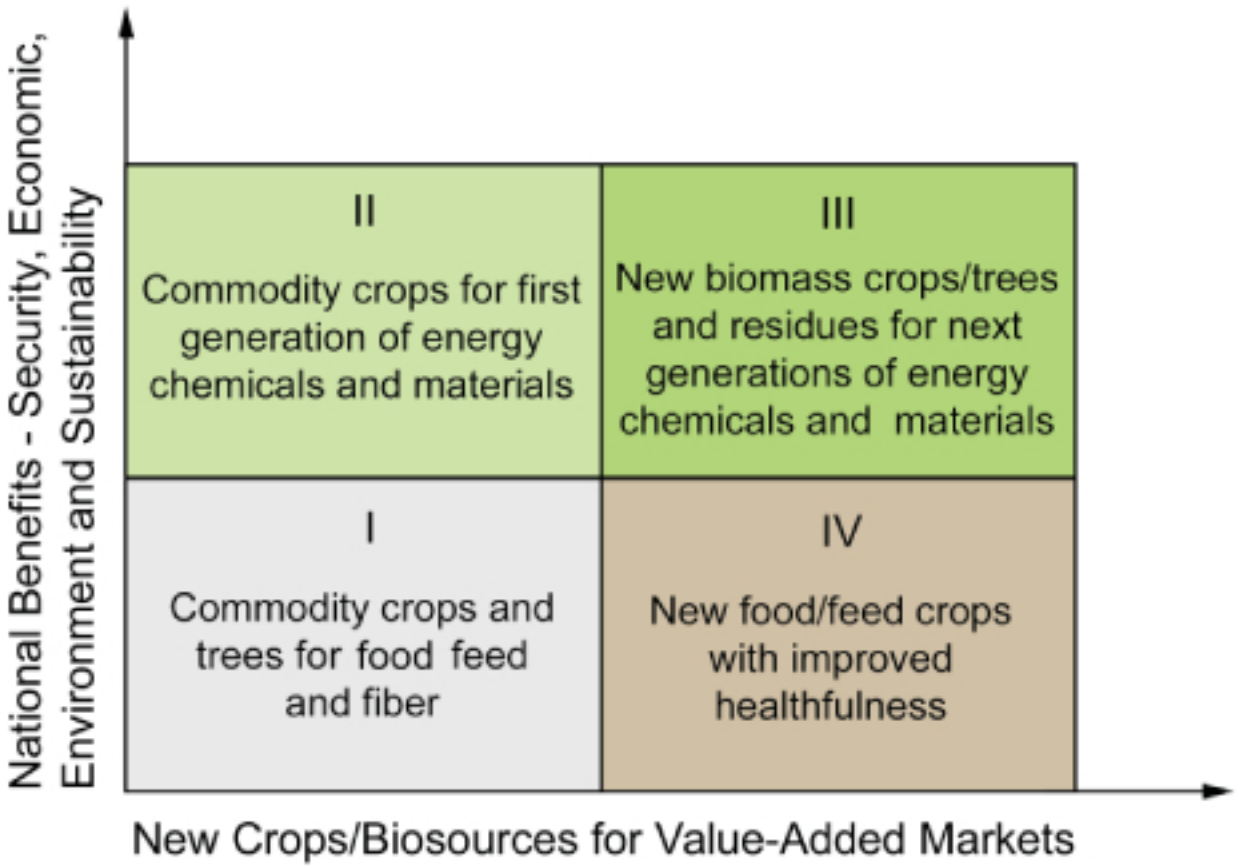
- *Agriculture and Forestry for Energy, Chemicals and Materials, The Road Forward*, which addresses agriculture and energy
- *Food and Agricultural Research: Innovation to Transform Human Health*, which addresses agriculture and health
- *Agricultural Water Security: Research and Development Prescription for Improving Water Use Efficiency Availability and Quality*, which addresses agriculture and water
- *Agriculture and the Changing Climate*, which addresses agriculture and global warming.

In addition, we are providing our *Vision for Agricultural Research and Development in the 21st Century*, which was the basis for Executive Order 13134, *Developing and Promoting Biobased Products and BioEnergy*, issued by President Clinton in 1999.

For further information, please contact Ralph W.F. Hardy, President of NABC, [redacted].

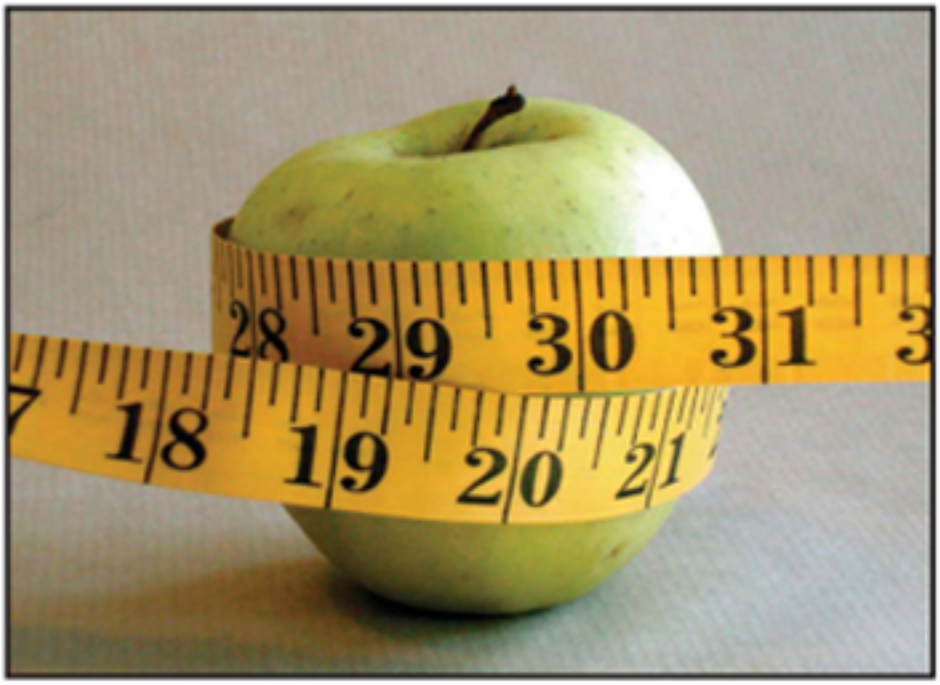
http://nabc.cals.cornell.edu/pubs/The_Road_Forward.pdf

Agriculture and Forestry for Energy, Chemicals and Materials: *The Road Forward*



http://nabc.cals.cornell.edu/pubs/AgFood_web.pdf

Food and Agricultural Research: Innovation to Transform Human Health

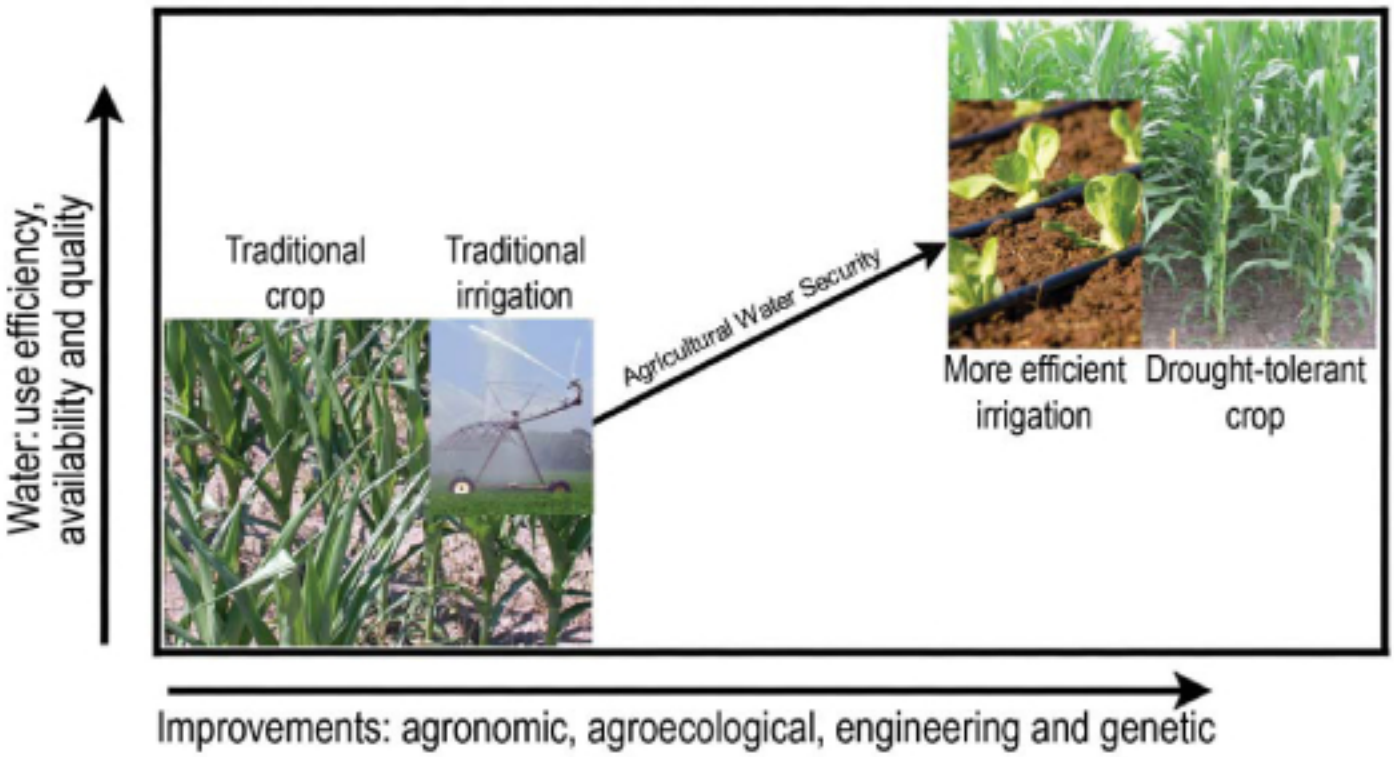


- The role that food plays in human health is historic and broad. "Let your food be your remedy," attributed to Hippocrates 24 centuries ago, and "an apple a day keeps the doctor away" both encapsulate the food-health relationship.
- A 21st-century plan to make food and agriculture a full partner in human health is proposed. It builds on multiple seminal contributions to key treatment advances from research in food and agriculture, and expands low-cost approaches and quality-of-life benefits by mitigating diet-related diseases.
- A 10% reduction in healthcare costs would save over $200 billion every year.

NATIONAL AGRICULTURAL BIOTECHNOLOGY COUNCIL

http://nabc.cornell.edu/pubs/WATERandAGRICULTURE.pdf

Agricultural Water Security: Research and Development Prescription for Improving Water Use Efficiency, Availability and Quality[1]



"Water is the staff of life."

—Traditional saying

"Our water crisis should occasion grave concern but not panic. We have solutions available; now we need a national commitment to pursue them."

—Robert Glennon (2009)[2]

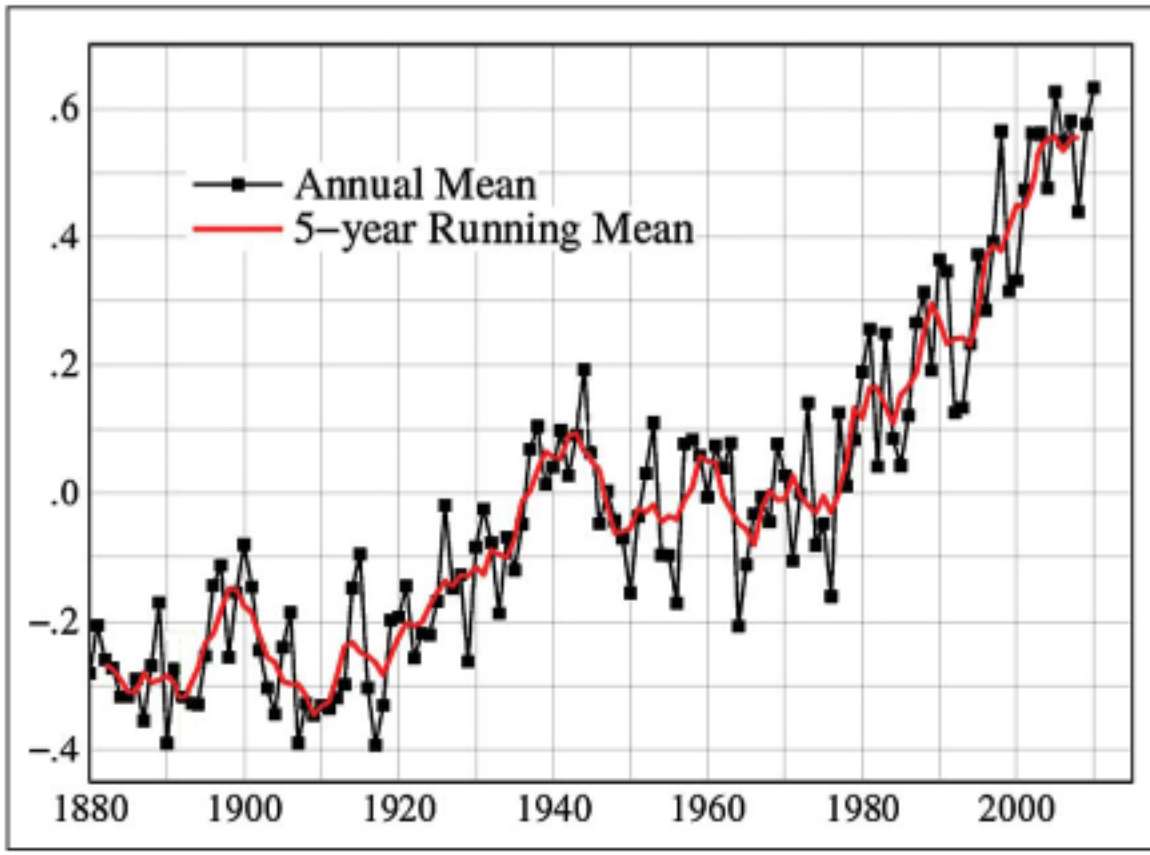
[1] In Canada and the United States.

[2] Glennon R (2009) Unquenchable: America's Water Crisis and What To Do About It. Washington, DC: Island Press.

Photographs by permission of: (crops) Drs. Kevin Steffey and Michael Gray (University of Illinois at Urbana-Champaign and the University of Wisconsin-Madison); (irrigation systems) Dr. H. Perlman (US Geological Survey) and iStockphoto LP.

http://nabc.cals.cornell.edu/Agriculture_and_the_Changing_Climate.pdf

Agriculture and the Changing Climate[1,2]



Global annual and 5-year running-mean land-ocean temperatures relative to the 1950–1980 mean.[3]

- *Climate change is occurring,* e.g. *Earth is warming.*[2]
- *Over the past 50 years, global research investments to increase agricultural productivity have simultaneously reduced carbon emissions at low cost compared to prior periods.*[4]

[1] Eaglesham, A. and Hardy, R.W.F. NABC Report 21: Adapting Agriculture to Climate Changes. Ithaca, NY: National Agricultural Biotechnology Council (2009). http://nabc.cals.cornell.edu/pubs/pubs_reports.cfm#nabc21.

[2] National Research Council. Advancing the Science of Climate Change. Washington, DC: National Academies Press (2010).

[3] NASA Goddard Institute for Space Studies. GISS Surface Temperature Analysis (2011). http://data.giss.nasa.gov/ gistemp/graphs/.

[4] Burney, J.A., Davis, S.J. and Lobell, D.B. Greenhouse gas mitigation by agricultural intensification. PNAS 107(26) 12052–12057 (2010).

http://nabc.cals.cornell.edu/pubs/vision.cfm

Vision for Agricultural Research and Development in the 21st Century

Biobased Products Will Provide Security and Sustainability in Food, Health, Energy, Environment, and Economy

Prepared by the National Agricultural Biotechnology Council

Office of Science and Technology Policy
Request for Information: Building A 21st Century Bioeconomy

Dear OSTP,

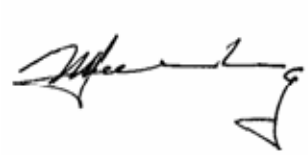
The Biomass Coordinating Council (BCC) would like to submit this document in response to the OSTP Request for Information: Building A 21st Century Bioeconomy.

The BCC is a Program of the American Council On Renewable Energy (ACORE), a 501(c)(3), non-profit organization based in Washington, D.C. The BCC has over 130 members and biomass stakeholders, including private sector biomass companies, trade organizations, universities, non-profits, financiers, and law firms. The BCC works to accelerate the adoption of renewable biofuels, bio-power, biothermal, biogas and bio-based products into mainstream American society through work in policy initiatives, convening, networking, and communications.

In working with our members, the BCC has prepared the responses below at the request of OSTP.

For questions or additional requests, please contact Taylor Marshall, BCC Program Director at marshall@acore.org or 202-507-4632.

Sincerely,



Bill Holmberg
Chairman, BCC

Taylor Marshall
Program Director, BCC

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In working with our members, the BCC has prepared the responses below at the request of OSTP.

(1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non- profit organizations, foundations, and other stakeholders to achieve this goal.

To create the bioeconomy of the future, the United States must commit to something similar to a Sustainable Industrial Revolution (SIR), embracing many of the concepts and technologies advocated by Jeremy Rifkin's Third Industrial Revolution, Amory Lovins' Reinventing Fire, and scores of books and major pronouncements calling for dramatic redirections of our society.

The backbone of the envisioned SIR is the full range of biomass industries: Food, Feed, Fiber, Fuel, Fertilizers and Feedstocks for chemicals/bio-based products – the 6 Fs. Readily available and sustainable biomass resources in all forms are critical in meeting the full range of potential needs of the 6Fs. There is no question about major opportunities for affordable biomass, the availability of commercialized or advancing technologies, the creativity to develop new uses, and the need to replace fossil fuels to reverse the build-up of greenhouse gases.

Restraints are manifested in ineffective land use, poor soil vitality and water shortages. There are good models in Europe and elsewhere. New York City is developing a custom declaring that if "you can see dirt, plant something." Parks and gardens, including roof top gardens and greenery, are increasingly being used as means to limit storm water run off, increase the efficiency of wastewater treatment plants, and moderate temperatures in cities. These and other measures should be priorities in boosting the production of biomass, increasing the vitality (and CO_2 absorbing capability) of the soil and using water more effectively.

These are the challenges to the scientific community, as well as to better recognize the contributions of nature (microbes, earth worms, dung beetles, compost, etc.) and the protection of wildlife that should be orchestrated by OSTP.

These biomass industries harbor three building blocks to the SIR. They are:

1. "Reindustrialization" of America through the sustainable modernization of cities and towns, and the sorely needed development of a comprehensive infrastructure serving the nation;
2. Creation of "New Wealth," with major economic and job creating multipliers, by focusing on the use of natural resources (extracted and sustainable, provided by nature at no cost thereby generating New Wealth, as opposed to service industries that rely on New Wealth or money mostly borrowed by the U.S.); and,
3. Creative collaboration between the extractive industries (using oil, gas, coal, minerals, metals, etc.) and sustainable industries (involving agriculture, forestry, all the renewables [solar, wind, biomass in all forms, hydro and water power, geothermal, and renewable hydrogen]), energy efficiency, recycle/reuse, and human creativity (built upon education, the driving power of an enlightened society).

Creative collaboration between the extractive and the sustainable industries is absolutely essential to overcome or bypass the many obstacles forged by malfunctioning governmental and financial institutions, too often responding, in an unenlightened/unsustainable way, to the power of paper and digital money.

Although reindustrialization is initially envisioned as the production of important products for the home and international market, it is critical to look beyond conventional living and to start restructuring our way of life – a sustainable way of life. In doing so, we must understand the importance of generating New Wealth and job creation focusing on the use of natural resources. Too often, we focus on "products" – important or just sellable. Instead, we need to focus on homes, buildings, streets, roads, highways, bridges, railroads, mass transit, etc. They are all mostly made from natural resources; they generate New Wealth with major economic multipliers and create jobs – and are essential to our future.

When the generation of New Wealth is well balanced and our financial and governmental systems are in order, we can maintain the most powerful military in the world, assist other nations, provide services needed by the populace to maintain order, deal with fire and other emergencies, offer quality health care and education, and reduce poverty along with our national debt.

Modifying and tweaking the current system will simply take us further into debt and consternation.

We need to aggressively turn to rebuilding our municipal areas, cities, towns, and our infrastructure – and our countryside with all of the externalities fully in mind (health care, climate change, education, order, natural systems, etc.) with the industriousness, commitment, and integrity essential to the times. The following sections detail this reindustrialization more specifically.

Biomass to the Rescue

Every city, town and community needs food. There is a rising movement to grow food locally. This can be done in schoolyards, backyards, rooftops, communities, greenhouses, window boxes, etc, and on local farms, using organic practices when appropriate. This is being reinforced by understanding that processed foods containing excess fats, sugars, and salt are causing obesity and other health problems, whereas fresh fruits and vegetables improve health. In cities, this is reinforced by the planting and maintaining of trees, plants, flowers, and other growing things to reduce storm water run off, moderate temperatures, provide beauty and comfort, and reinforce the human/natural systems relationships – and grow more biomass for the 6Fs while absorbing more CO_2.

Biomass should be planted, grown and nurtured on lands that are contaminated, misused or underutilized involving optimized land management, soil vitalization, and water conservation. We must recognize that biomass is the basis for all three of the major carbon sequestering sectors – soil, biomass, and the oceans (through preventing run off by wetlands, watersheds, and riparian buffers). Biomass in all forms – food, feed, fiber, fuel, fertilizers, and feedstocks for chemicals/biobased products – are major business for domestic and international markets as well as big job-producing industries that lend themselves to small, community-based operations).

Experiential Education

Experiential education should begin in preschool and continue into K-12. Classes and activities will incorporate growing gardens in school yards, back yards, communities, roof tops, greenhouses, and window boxes; and, trees, bushes, and grasses would be planted and cared for wherever possible to beautify, shelter, save/produce energy, enhance the environment, and save water while reducing carbon footprints. Appropriately-scaled, wind, solar, geothermal (ground water heat pumps) technologies and energy efficiency, would also be incorporated; along with a good understanding of conventional forms of energy – oil, gas, coal, nuclear, etc – and their importance. The concept is to incorporate hands, eyes, minds, work, sharing/giving, and emotions into the study of reading, writing, arithmetic, science, social studies, etc. Physical involvement and creativity would produce food to eat and greenery to enjoy while understanding the benefits of good diets, and how to use and create methods and technologies to serve school, family, community, and country.

Prisons, Veterans, and Biomass

Prisoners working, learning, and being trained in conservation camps (along the lines of the Civilian Conservation Camps) instead of in jails and prisons will save an enormous amount of public funds, reduce recidivism, and build character; with workers benefiting from the therapeutic effects of outdoor living and working with natural systems. Veterans, with leadership skills and dedication to country can be retrained to lead in these nation-building (humans and nature) efforts.

Veterans and biomass can be combined to accelerate our race to the future bioeconomy. In the U.S., the farming population is aging, but the cost of land and equipment are major deterrents for startup conventional agricultural enterprises. However, there will be a plethora of opportunities stemming from modern science and technology to place veterans and their families in the food and energy business. School yard, backyard, roof top, community-based gardens; greenhouses; small biogas, biofuels, and composting operations; smaller solar and wind projects as well as ground water heat pumps; holistic farming and gardening; and many other connected opportunities are emerging to provide "hortatherapeutic" and financial opportunities for veterans and their families.

Transportation

The United States is primarily focused on over-the-road vehicles, planes, and trains (primarily for cargo – metros for passengers). Internal combustion engines and fossil fuels (with the emergence of alternatives) dominate our transportation sector. Fortunately, revolutionary changes in both engines and alternative fuels are underway. Ethanol and biodiesel have provided the foundation for alternative fuels in the U.S., producing over a million barrels of gasoline equivalent a day. Additionally, the biofuels industry is transitioning to waste streams, cellulosic materials, and algae. The efficiency of growing and converting grains and oil seeds to biofuel continues to advance at a steady pace. Distiller's grains, subject to cooking, enzymatic treatment, and high temperatures, more easily passes through the rumen of monogastric animals, leaving more energy for weight gain – a boost in efficiency in the production of ethanol from grains.

Tangentially, automakers are being required to advance existing technologies and pursue breakthroughs into new engine concepts to meet increasing mileage standards. This routinely requires higher compression ratio engines and higher octane fuels. Also, because of diminishing oil reserves, which are concentrated in nations not favorably inclined to the U.S., there are pressing requirements for more domestically-produced, efficient and cleaner burning, higher-octane transportation fuels.

After lead and then methyl tertiary butyl ether (MTBE) were banned, refiners turned to aromatics (BTX – benzene, toluene and xylene) at about 24% and ethanol at 10% to meet octane needs of today's vehicles. Depending on the cost of their respective feedstocks – oil/tar sands/oil shale; and corn for the near term and cellulosics/algae into the future – the cost between BTX and ethanol to the public should be roughly comparable. Therefore, national/energy security, environmental and healthcare costs should be the determining factors. BTX will mostly come from imported oil; ethanol is produced here at home. BTX is fossil based; ethanol is renewable, with a routinely smaller carbon footprint. In addition to comparably more ozone precursors in emissions from the combustion of BTX, there are also the most troubling ultra fine particulates (UFP). These minute bits of solid carbon coated with PAHs and quinones enter into the bloodstream through the lungs of people, particularly those living in high traffic congested areas. This is particularly alarming when these coated UFPs pass into the blood stream from a mother to the fetus causing disruption in genetic codes leading to diseases like asthma,

autism, cancer, and other dangerous maladies. It has been reported that UFP lead to about $100 billion a year in added health care costs.

Dr. Eddie Sturman, president of Sturman Industries, is advancing the internal combustion engine to a revolutionary stage. He is convinced that biofuels are the fuels of the future, with levels of efficient to fully offset the BTU content of ethanol (76,000 BTU versus 120,000 for gasoline). Ethanol is not toxic, with much cleaner burning and essentially little or no UFP.

Although higher levels of ethanol (say 30% to meet the octane needs of advanced engines while reducing evaporative emissions) somewhat increases aldehyde emissions, they are of little consequence compared to the deadly emissions of BTX. There is sufficient scientific information available to verify this information. What is needed now is a massive public information campaign to alert the nation to the economic, national/energy security, environmental, and public health choices now before the government and the congress in meeting the octane needs of the transportation sector.

Status quo transportation fuel advocates will claim the need for more information. Others state that there is more than enough data to justify corrective action by the EPA. The great importance of this issue warrants action based on existing facts, rather than more delays that seriously threaten our public health, national/energy security, our economy, and our environment. A recent Wall Street Journal article (November 8th, 2011) has shed light on the issue. There are floodlights of available information that must now enlighten the American people.

Federal Establishments Leading the Charge

The Department of Defense has made great strides in incorporating renewable energy into their operations, and their optimization of land for the production of biomass for biopower, biofuels, and other products can serve as a model for other sections of the US government. Their major contribution is their commitment to a cultural change that incorporates energy, humans, power and weapons systems as a top, interlocking priority.

The Sustainable Industrial Revolution is the vision for the bioeconomy of the future. Below, we have listed several other examples of specific steps that can be taken to accelerate the bioeconomy of the future.

(2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

Although a portfolio of solutions will be necessary to update our degraded, inefficient, and unclean transportation sector, "drop-in" fuels made from renewable biomass that can integrate with the existing energy infrastructure represent a particularly high-impact research area.

Research that aims to utilize, value, and care for our carbon / our resources most effectively would create the most impact by building a new foundation for the bioeconomy of tomorrow on the lessons learnt through our long agricultural history. For example, a national panel led by Iowa State University is launching an effort to research and develop technologies that capture, use and sequester carbon while enhancing food production, ecosystems, economic development and national security. A parallel effort should be increasing research and data analysis to determine the efficiency of replacement, minerals, microbes, macrobes, compost, and biochar to vitalize soil.

(5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

Allow government researchers, individually or in concert, to continue their lab work after hours to engender a private enterprise. In addition, the House has passed legislation (The Entrepreneur Access to Capital Act; H.R. 2930) to provide funds to support crowd-endorsed research and business start-ups. The legislation "creates a crowd funding exemption from SEC regulations for firms raising $5 million, with individual investments limited to $10,000 or 10 percent of an investor's annual income, whichever is lesser." Anything that the white house could to keep crowd financing from being prohibitively expensive could greatly aid technology in crossing over the first "valley of death" and into pilot stages. Bioenergy and biomass technologies, in particular, could benefit because many can be tested and implemented at a lower cost than non-biological projects.

(6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?

The use of such investor funding criteria as listed below would accelerate commercialization:

•*Proof of concept*

–It is essential to have clear evidence of proof of concept on a pilot or demonstration scale 10% of full scale for example (as opposed to just lab scale)

–Investors ask about key performance metrics – yield, productivity, etc. – and how close current figures are to commercially required levels

•*Roadmap to profitability*

–Investors expect to see a credible and transparent roadmap to production scale-up and ultimately positive cash flow and profitability

–This entails, among other things, adequate detail on: (1) target production economics; (2) cost of capacity expansion and how it will be funded; and (3) timing of scale-up and cost reduction plans

•*Strategic partners*

–Industry partnerships serve one or more of these purposes: (1) direct financial support for capacity expansion; (2) off-take agreements; and, in a more intangible sense; and (3) "a blue chip seal of approval"

–Given that partnerships can also limit room to maneuver, investors should ask about exclusivity provisions in partnership agreements

•*Access to feedstock*

–If it is conventional feedstock, can it be obtained at preferential pricing, and are long-term supply contracts a viable option?

–If it is cellulosic feedstock, is the pricing structure clear?

(7) What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

The biomass industry faces a major challenge over issue of indirect land use change (ILUC). More ILUC information can heighten sustainable practices in the biomass industry while informing the public about realistic, not uncertain and alarmist, environmental impacts. The following statement is from an ORNL/CBES workshop report: "In most cases, the uncertainty in the land-use databases themselves is tremendous. For example, differences between baseline measures for the same time and place in different databases may be larger than the observed changes. Therefore, the quality of input data to scenario studies is an issue of considerable importance, because it could have a potentially large effect on the scenario outcomes. To complicate the situation further, some data sets necessary for validation are available only at high cost, some are not publicly available, and the most useful information, such as causal factors of deforestation, simply has not been collected."

(8) What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

Existing private-sector models of venture funding typically seek to maximize financial profits and return on capital in contrast to forms of social and environmental entrepreneurship pursuing a triple bottom line (with people, planet, profits or economic, social, and environment as criteria) or "entrepreneurship in service of the whole" which seeks to realize a quintuple bottom line by growing natural, social, economic, cultural, and spiritual capital. A thriving entrepreneurial bioeconomy fundamentally requires

entrepreneurs and their financiers to commit to a triple, or better yet, a quintuple bottom line thereby addressing the fundamental and systemic failures of an economic system which usually excludes the bios, or that which gives life and sustains us. The challenges of financing an entrepreneurial bioeconomy are thus related to the design and implementation of an enabling financial infrastructure that provides bioeconomy entrepreneurs and their investors with sufficient incentives, rewards, and opportunity to provide authentic and creative leadership to enterprise development which focuses on balanced growth of multiple forms of capital and is not limited to the pursuit of short term economic profitability. A bioeconomy financial infrastructure also needs to recognize the importance of community and engagement of the crowd as a critical success factors for its emergence and long-term sustainability.

Specific steps agencies can take to address the above challenges are the following:

- *Define* entrepreneurial bioeconomy enterprise as "entrepreneurship in service to the whole" i.e. any and all activities seeking to meet the needs of the present generation without compromising the ability of future generations to meet their own needs by creating organizations as living systems in alignment with nature so all life will flourish forever; and, by generating Profits4Life – flows of positive natural, social, economic, cultural, and spiritual capital
- *Jumspstart and mainstream* the entrepreneurial bioeconomy by supporting entrepreneurship in service of the whole with an enabling set of fiscal, financial, and regulator incentives designed to lower perceived risks (early stage enterprise risks in particular), including but not limited to:
    - *Establishing* sound regulatory frameworks by creating incentives and removing barriers.
    - *Prioritizing* government investment and spending in areas that stimulate the entrepreneurial bioeconomy.
    - *Limiting* spending in areas that deplete natural and other forms of capital
    - *Employing* taxes and market-based instruments to shift consumer preferences and promote investment and innovation in the bioeconomy.
    - *Investing* in capacity building and training.
    - *Strengthen* international governance.
- *Stimulate* entrepreneurship in service of the whole as well as community engagement and wisdom of the crowd by means of public sector matched-funding mechanisms which amplify and leverage sponsorships, donations, and investments provided by people and organizations to initiatives of their choice through emerging crowd funding mechanisms and legislation.
- *Launch* whole system enterprise development zones throughout the nation as pilot initiatives of the emerging bioeconomy and linking them to existing centers of excellence of technological, educational, industrial, agricultural and community revitalization.

(13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

A unified, liquid energy "molecules are molecules" chemical view needs to be adopted by regulating agencies such as the EPA. For example, a Biomass Coordinating Council member company that makes a renewable gasoline from biomass has applied to the EPA for a "substantially similar" certification. However, the company has not yet received approval to move forward due to the fact that ASTM specifications require gasoline to be derived 100% from petroleum. The company is denied because they are biomass-based, although their product is chemically identical to petroleum (99.98%) as shown by both mass spectroscopy and gas chromatography.

(14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

Transparency is necessary with regards to where a new company request sits in the queue for being evaluated as a technical priority. "Black hole" timing at agencies like the EPA is impeding progress. Additionally, improving patent protection and timing with the USPTO is critical so that U.S. innovation can make a comeback in a global environment.

(16) What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

The US has a long history in enabling break-though innovations and lasting prosperity by means of an enabling environment for creativity and entrepreneurship. By 2025 fifty percent of the world population will be 25 years old or less. Their future is ours. The bioeconomy is an emerging sector within the world economy that will define humanity's success or failure in meeting the needs of present generations without compromising the needs of future generations. Successful development of the entrepreneurial bioeconomy and US leadership with respect thereto will require the coming together of public and private sector partners from the local to the global to collaborate within an overarching framework that enables investment and entrepreneurship in service of the whole. The highest impact opportunities are those partnerships that reinvent and realign the prevailing economic, business, and financial model from an integrated systems perspective and enable the fast emergence of the entrepreneurial drive and creative solutions that will provide a solid foundation for a thriving bioeconomy. There is no need to pick winners other than to create the enabling conditions for winners to emerge along the lines proposed in 5 and 8 above. Of all imaginable public-private partnerships, potentially the most influential one is a public-private partnership between government, business, and the community of citizens (a crowd sourced for talent, matched funding, and collective wisdom).

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December 5, 2011

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Submitted electronically to: bioeconomy@ostp.gov www.regulations.gov

Re: Request for Information: Building A 21st Century Bioeconomy, published in the October 11, 2011 *Federal Register* (76 FR 62869)

The Association of American Medical Colleges (AAMC) is pleased to have this opportunity to comment on the Request for Information entitled *Building a 21st Century Bioeconomy*, issued by the Office of Science and Technology Policy (OSTP).

The AAMC is a not-for-profit organization representing all 136 accredited U.S. and 17 accredited Canadian medical schools; nearly 400 major teaching hospitals and health systems, and nearly 90 academic and scientific societies. Through these institutions and organizations, the AAMC represents 128,000 faculty members, 75,000 medical students, and 110,000 resident physicians.

We are pleased to see the Executive Office address the critically important topic of translating the country's innovations in biological research to meet the challenges our nation faces. Below we address some of the questions posed by OSTP as it works to develop a National Bioeconomy Blueprint.

As a general comment, we note that the examples of new research opportunities provided by the RFI, and the general framing of the document, appear to imply that the 21st Century Bioeconomy will be mainly driven by laboratory-based research translated into largely commercial applications. The AAMC agrees that bench research will continue to be a major driver of the new economy. However, profound discoveries and implementation of research findings also take place in a variety of other places, including clinical delivery settings and in communities, ensuring fidelity with the social contract that the benefits of research will be used to improve health and develop sustainable health delivery systems for all Americans. The AAMC, which focuses on improving health for all, advocates for support of research across the full continuum of health sciences, from basic biological research to implementation science, health services research, etc. This continuum involves biomedical, social, behavioral and other sciences, and, as the RFI indicates, is increasingly transdisciplinary and team-oriented.

Grand Challenges

> **Description from OSTP:** President Obama has identified "grand challenges"' as an important element of his innovation strategy, such as "smart anti-cancer therapeutics that kill cancer cells and leave their normal neighbors untouched; early detection of dozens of diseases from a saliva sample; personalized medicine that enables the prescription of the right dose of the right drug for the right person; a universal vaccine for influenza that will protect against all future strains; and regenerative medicine that can end the agonizing wait for an organ transplant."'

The institutions represented by the AAMC perform more than half of all extramural research sponsored by the National Institutes of Health (NIH), and also conduct research supported by other federal agencies, industry and philanthropy. We note that major scientific challenges inevitably have implications for resources and infrastructure. In fact, many areas of biomedical science are becoming increasingly dependent on large scale instrumentation, facilities and infrastructure, similar to how the physical sciences came to rely on such infrastructure in the 20th Century. Major challenges should therefore include development of new resources that can support life sciences broadly. Two examples would be the development of new biomarkers for disease, and new disease models. Improvement in information systems and the broad use and integration of electronic medical records into research would be a substantial benefit to innovation in health care.

Research and Development

> **Description from OSTP:** R&D investments, particularly in platform technologies, can support advances in health, energy, the environment, and agriculture, and accelerate the pace of discovery in fundamental life sciences research.

The AAMC strongly agrees with the premise of this section, and the increasing opportunities for developing platform technologies. Moreover, such development often focuses on technologies that are "precompetitive" and would permit more extensive partnerships involving industry, academic institutions, governmental agencies and non-profit organizations.

A particularly ripe area for precompetitive collaboration is in the effort for establishing valid biomarkers for slow developing diseases. The current effort led by researchers from NIH's National Institute on Aging, industry and academia to develop quantitative disease models by sharing data from Alzheimer's Disease patients shows great promise. As an Institute of Medicine panel recently noted, "Collaboration on data, resources, and biological specimens could lead to significant advances in the development of genomic and genetic applications. However, intellectual property protections and other barriers can inhibit or outright prevent these collaborative efforts." To the extent possible, federal regulations and policies should promote these collaborations.

Federal policies should also promote the use of shared research facilities, instrumentation, and other resources, both regionally and remotely. Resource sharing helps promote efficiencies in construction, maintenance, and operation of, for example, expensive core facilities. As noted above, much biomedical research relies on advanced technologies, informatics, and emerging tools, as well as on shared research resources that often require dedicated professional staff. Growth in transdisciplinary research - and the increasing need for investigative teams with diverse and specialized skills and capabilities - also further complicates the management of science. The very process for using shared resources can help promote collaboration among investigators, and may help promote team science. The extraordinarily productive use of DOE-funded synchrotron radiation facilities to support biological structure investigations is a model in this regard. Other potential models of collaboration involving the use of shared infrastructure include the NIH Clinical and Translational Science Awards (CTSA) program, which is developing national consortia for clinical investigation. CTSAs also link with other established resources and programs, including for example pioneering programs in clinical effectiveness and health outcomes research in the Department of Veterans Affairs.

Moving Life Sciences Breakthroughs From Lab To Market

> **Description from OSTP:** It is a challenge to commercialize advances in the life sciences because of the risk, expense, and need for many years of sustained investment. The Administration is interested in steps that it can take directly, but is also interested in encouraging experimentation with new private-sector-led models for funding commercialization of life sciences research.

The AAMC believes that the Bayh-Dole Act and other federal policies promoting technology transfer already provide an excellent framework to facilitate transfer of technology from academic institutions into useful application. Recent joint comments by the AAMC, the Association of American Universities, and other higher education associations to the Department of Commerce, noted that a major limitation for university transfer of technology is faculty's lack of access to funding for proof-of-concept research, market analysis, or appropriate mentoring. To address this situation, the associations recommended the establishment of new "Translational Supplemental Awards."

> These awards would be made by the major federal research agencies to support proposals jointly submitted by an existing principal investigator and the university TTO or another appropriate institutional research or technology commercialization official. These awards would be made at the tail end of federally funded awards to support next stage research for projects that show strong clinical or market potential. We believe that providing such awards would both incentivize researchers to think about the potential commercial applications of their research and help to change the culture of the federal research agencies in ways that would help facilitate the commercialization goals of the Administration. (AAU et al, April 1, 2011)

Workforce Development

> **Description from OSTP:** Investment in education and training is essential to creating a technically-skilled 21st century American bioeconomy workforce.

Biomedical and health science training, both through training programs and research project grants, not only creates environments for trainees to develop in-depth discipline-based expertise, but should also help prepare trainees for a broad diversity of careers, including industry, public policy, and other areas, all of which potentially contribute to health and medicine. The AAMC supports high quality education and training for all research trainees and recognizes the need for early exposure to and training for a broad range of career options, including those outside of academic research. A successful graduate of a training program, along with acquiring scientific research skills, would acquire professional and career development skills, such as effective communication, collaboration, and leadership. In addition, training programs should include a team-based focus and encourage interdisciplinary training and collaborations, as increasingly, young scientists train to work in teams and in collaborations on cross-disciplinary research.

Although beyond the scope of AAMC's core constituency, AAMC recognizes the important role that community colleges play in training the science and engineering workforce. In addition, the AAMC recognizes that the science workforce goes beyond researchers to include all members of a team - the business advisors, core facility specialist, pharmacists, nurses, and physician assistants. Community colleges, undergraduate programs and graduate education all have critical roles to play in preparing students for the broad expertise that is needed in the research workforce of the 21st century.

Training future scientists and engineers also requires partnerships with the private sector. As noted above, many trainees will go into careers in the private sector. The AAMC proposes that prospective employers, including those from the private sector, inform academic training programs of the knowledge and skills that they value in trainees and recommend training needs so that trainees are better prepared to enter the workforce. In addition, AAMC recommends that the private sector develop more training opportunities, in the form of internships and fellowships, for students and postdocs. For example, the National Science Foundation's program for Integrative Graduate Education and Research Traineeship (IGERT) provides an excellent model for exposing trainees to opportunities for collaboration and application of research to social needs.

Reducing Regulatory Barriers To The Bioeconomy

> **Description from OSTP:** As President Obama has stated, our regulatory system must "identify and use the best, most innovative, and least burdensome tools for achieving

> regulatory ends" and "protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation."

The AAMC is supportive of this administration's efforts to review and reduce regulatory burden. In addition to looking at the overall burden of any regulatory process, we believe that it is essential to assess whether the regulatory burden at any level is supported or justified by the resulting benefit or success of the regulation in accomplishing an agency's stated goals. To accomplish this objective, the evaluation of existing regulations should include assessment of both the burden placed on researchers and institutions and clear metrics to evaluate success. More importantly, the text of new regulations should embed mechanisms and metrics to review their burdens and effectiveness.

Of primary concern in the highly-regulated environment of biomedical research is whether new regulations are based on solid evidence that the proposed change will adequately address regulatory concerns while allowing ethical, scientifically sound research to continue. This "evidence-based regulation" not only increases the chances that the agency goals will be achieved, but also promotes compliance and public trust that the regulations are the result of evidence that supports their adoption. For example, in the final rule on financial conflicts of interest (Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought, 42 CFR Part 50 Subpart F), the definition of a Significant Financial Interest that must be disclosed by an investigator to an institution includes certain remuneration or equity interests with a value of $5000 or more. The rules that have been in effect since 1995 set that same *de minimis* threshold at $10,000. The decreased threshold will substantially increase the number of disclosures institutions will have to collect and review, but was not supported by data that indicated the need for or likely effect of the change on the objectivity of research. It may be that the increased burden borne by institutions and researchers is justified by the effect of such disclosures on research objectivity, investigator behavior, or public trust, but we cannot know without setting both the expectation and the process for assessing the impact.

Public-Private Partnerships

> **Description from OSTP:** The Administration is interested in serving as a catalyst for public-private partnerships that build the bioeconomy and address important unmet needs in areas such as health, energy, agriculture, and environment.

AAMC recognizes that the realization of the promise of biomedical research requires the development and fostering of principled partnerships between academia, industry, government, and communities (for example, see our comments on precompetitive technology and biomarkers above). Particularly with regard to the translation of promising therapeutics from the bench to clinical practice, the facilitation of such partnerships is a critical role for the government. The bioeconomy needs the input from all stakeholders, including the academic medical centers and teaching hospitals to remain competitive on a global scale. By establishing roadmaps and support for the productive, ethical collaboration between the public and private sectors, the

Administration can both set expectations and increase public trust in the U.S. Research enterprise.

We would be pleased to offer OSTP further assistance in this important process. The AAMC has long been an advocate for the improvement of health of all through discovery and has provided federal agencies and administrations with specific comments on many of the topics summarized here and related comments about the development of a research workforce, the regulation of research, and the importance of preparing for the research needs of the future. I invite you to visit our website if you would like additional information on these topics [insert testimony and correspondence page here] and please do not hesitate to contact me with any questions.

Sincerely,

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December 6, 2011

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Re: FR Doc. 2011-26088
Request for Information: Building a 21st Century Bioeconomy

Dear Dr. Holdren,

Thank you for the opportunity to submit comments on behalf of the Alliance for Aging Research to help inform the Office of Science and Technology Policy (OSTP) as it develops a National Bioeconomy Blueprint. The Alliance for Aging Research is a nonprofit group that has advocated for 25 years in support of research to improve the quality of life and health for all Americans as they grow older. Our efforts have focused largely on federal funding of research by the institutes and centers that comprise the National Institutes of Health (NIH) because of the important role they play in facilitating aging-related research.

We understand that the National Bioeconomy Blueprint will outline Administration-wide steps to harness biological research innovations to address national challenges in health and other critical sectors. We share the Administration's recognition that research underpins the foundation of a significant portion of the US economy and we believe that it is essential to overcoming one of the most pressing challenges facing our country--the aging of our population.

In January of this year, the first of the baby boomers began turning age 65. Older Americans now make up the fastest growing segment of the population. According to the U.S. Census Bureau, the number of people age 65 and older will more than double between 2010 and 2050 to 88.5 million, or 20 percent of the population; and those 85 and older will increase three-fold, to 19 million. Late-in-life diseases such as type 2 diabetes, cancer, neurological diseases, heart disease, and osteoporosis are increasingly driving the need for healthcare services in this country. Many of these age-related diseases are expected to become more prevalent as the number of older Americans increases.

Currently, the average 75-year old has three chronic health conditions and takes five prescription medications. Six diseases--heart disease, stroke, cancer, diabetes, Alzheimer's and Parkinson's disease–cost the U.S. over $1 trillion each year. A report in the *Journal of Clinical Oncology* projected cancer incidence will increase by about 45% from 2010-2030, accounted for largely by cancer diagnoses in older Americans and minorities, and by 2030, people aged 65 and older will represent 70% of all

cancer diagnoses in the U.S. In the absence of new discoveries to better treat and prevent osteoporosis, it is estimated it will cost the U.S. $25.3 billion per year by 2025.

But research holds incredible promise. According to an Alzheimer's Association report from 2010, research breakthroughs that slow the onset and progression of Alzheimer's disease could yield annual Medicare savings of $33 billion in 2020 and as much as $283 billion by 2050. We feel that preventing, treating or curing age-related diseases, is perhaps the single most effective strategy in reducing national spending on health care.

David M. Cutler, PhD, of Harvard University completed a study in December of 2007 which showed that health near traditional retirement ages has improved markedly over time. His work found that people who were aged 62 in the 1960s or 1970s were in equivalent health to people aged 70 or more today. On the one had this is promising news because people in their 70s are living healthier and productive lives, unfortunately they remain vulnerable to diseases that occur in later ages for which there are no effective treatments and cures. Research that leads to a better understanding of the aging process' inherent human vulnerability to age-related diseases could be the key to helping Americans continue living healthier more productive lives longer.

Scientists who study aging now generally agree that aging is malleable and capable of being slowed. Rapid progress in recent years toward understanding and making use of this malleability has paved the way for breakthroughs that could increase human health in later life by opposing the primary risk factor for virtually every disease we face as we grow older—aging itself. Better understating of this "common denominator" of disease could usher in a new era of preventive medicine, enabling interventions that stave off everything from dementia to cancer to osteoporosis. As we now confront unprecedented aging of our population a modest extensions of healthy lifespan could produce outsized returns of extended productivity, reduced caregiver burdens, lessened Medicare spending, and more effective healthcare in future years.

While there has been great excitement surrounding recent progress in aging research, a large gap remains between promising basic research and healthcare applications, and closing that gap will require considerable focus and investment. We submit the following research agenda for consideration as a Bioeconomy Blueprint "Grand Challenge" to promote more focused research that could more quickly lead us to interventions that might extend human healthspan.

I.) Grand Challenge: *Slow Aging and Slow Disease*

Key research questions within four categories—cell replacement, inflammation, stress response, and tools & models—were chosen by a team of leading U.S. and European scientists with the goal of identifying some of the most promising research in the field. They have been endorsed by close to 70 leaders in the field. These questions identify a range of projects that, with sufficient funding and focus, are likely to yield significant progress within 3 to 10 years.

Cell Replacement

One hallmark of aging tissues is their reduced ability to regenerate and repair. Many tissues are replenished by stem cells. In some aged tissues, stem cell numbers drop. In others, the number of stem cells changes very little—but they malfunction. Little is currently known about these stem cell declines, but one suspected cause is the accumulation of "senescent" cells. Cellular senescence stops damaged or distressed cells from dividing, which protects against cancer. At advanced ages, however, the accumulation of senescent cells may limit regeneration and repair, a phenomenon that has raised many questions. Do senescent cells, for instance, alter tissue "microenvironments," such that the tissue loses its regenerative powers or paradoxically fuel the lethal proliferation of cancer cells?

A robust research initiative on these issues promises to illuminate the roots of a broad range of diseases and disabling conditions, such as osteoporosis, the loss of lean muscle mass with age, and the age-related degeneration of joints and spinal discs. The research is also essential for the development of stem cell therapies, the promise of which has generated much public excitement in recent years. This is because implanting stem cells to renew damaged tissues in older patients may not succeed without a better understanding of why such cells lose vitality with age. Importantly, research in this area would also help determine whether interventions that enhance cellular proliferative powers would pose an unacceptable cancer risk.

<u>Cell Replacement Key Research Questions</u>

- How, when, and in what tissue types are cells, including stem cells, typically lost during the aging process?

- In what organs and tissues is such loss beneficial, for instance, to avert cancer? How, when, and where are such losses detrimental, and what factors distinguish beneficial from detrimental loss?

- How do tissue microenvironments change with age in different organs? Are these changes caused by an accumulation of senescent cells? Do they reduce tissue/organ function?

- Do age-related changes in microenvironments deplete tissues of resident stem cells, foil circulating stem cells from proper "homing," or prevent stem cells from functioning? Or, are there age-related systemic (circulating) factors that are detrimental to stem cell function?

- Is it possible to "wake up" stem cells within the aging body via systemically administered compounds that alter microenvironments or neutralize detrimental circulating factors?

- Do individual cells change in random ways that cause them to be out-of-step with neighboring cells and therefore fail to contribute to normal tissue/organ function? Based on single-cell assays, what are the molecular determinants of random changes, cellular responses to such changes, and their consequences for tissue/organ function?

- In animals whose longevity has been enhanced by genetic, dietary, or drug interventions, what age-related cellular losses, changes in stem-cell function, shifts in cellular microenvironments, or random changes are delayed or prevented?

- Can markers of cellular senescence, which accumulate with aging, be used as biomarkers to monitor or predict the efficacy of anti-aging therapies, the pro-aging effects of environmental or lifestyle factors, or the biological age or healthspan reserve of individuals?

- How do specific, age-related changes in stem cells or microenvironments contribute to particular diseases of aging? How can these changes be reversed or neutralized?

Inflammation

Acute inflammation is necessary for protection from invading pathogens or foreign bodies and the healing of wounds, but as we age many of us experience chronic, low-level inflammation. Such insidious inflammation is thought to be a major driver of fatal diseases of aging, including cancer, heart disease, and Alzheimer's disease, as well as of osteoporosis, loss of lean muscle mass after middle age, anemia in the elderly, and cognitive decline after 70. Indeed, just about everything that goes wrong with our bodies as we age appears to have an important inflammatory component, and low-level inflammation may well be a significant contributor to the overall aging process itself. As the underlying mechanisms of age-related inflammation are better understood, researchers should be able to identify interventions that can safely curtail its deleterious effects beginning in mid-life—broadly enhancing later-life—and with negligible risk of side effects.

<u>Inflammation Key Research Questions</u>

- Which age-related changes in inflammatory pathways are most important for the heightened risk of diseases of aging?

- What role, if any, does age-related inflammation play in the loss of normal stem-cell function with age?

- Which inflammation-related sources of harm (that is, ones tightly linked to diseases of aging) are delayed or prevented by longevity-enhancing interventions, such as calorie restriction, or other interventions that enhance healthspan?

- Are age-related changes in the levels of certain inflammatory cytokines (chemical messengers secreted by immune cells) proximal causes for multiple diseases of aging? Do some such cytokine changes have little or no bearing on age-related diseases, or are some even beneficial (for example, because they compensate for an age-related decline in function)?

- What are the prime causes for age-related inflammation and changes in inflammatory cytokines? Do certain environmental toxins, microbial pathogens, or dietary components stand out as leading sources of detrimental, age-related inflammation?

- Can interventions with anti-inflammatory effects broadly lower risks of multiple diseases of aging? Might this be true in humans—for example, humans treated with anti-inflammatory compounds and monitored for illnesses the compounds weren't developed to treat, suggesting they may broadly enhance healthspan and possibly longevity?

Stress Response

A central theme in modern aging research—perhaps its "key" discovery—is that the mutations, diets, and drugs that extend lifespan in laboratory animals by slowing aging often increase the resistance of cells, and animals, to toxic agents and other forms of stress. These discoveries have two main implications, each of which is likely to lead to major advances in anti-aging science in the near future.

First is the suggestion that stress resistance may itself be the cause (rather than merely the companion) of the exceptional lifespan in these animal models, hinting that studies of agents that modulate resistance to stress could be a potent source of valuable clinical leverage and preventive medicines. Second is the observation that the mutations that slow aging augment resistance to multiple varieties of stress—not just oxidation, or radiation damage, or heavy metal toxins, but rather resistance to all of these at the same time.

The implication is that cells have "master switches," which like rheostats that can brighten or dim all lights in a room, can tweak a wide range of protective intracellular circuits to tune the rate of aging differently in long-lived versus short-lived individuals and species. If this is correct, research aimed at identifying these master switches, and fine-tuning them in ways that slow aging without unwanted side-effects, could be the most effective way to postpone all of the unwanted aspects of aging through manipulation of the aging rate itself. Researchers have formulated, and are beginning to pursue, new strategies to test these concepts by analysis of invertebrates, cells lines, rodents, and humans, and by comparing animals of species that age more quickly or slowly.

<u>Stress Response Key Research Questions</u>

- What changes in the stress response at the systemic, cellular, and molecular levels contribute to older animals' diminished stress resistance and elevated risk of serious disease?

- Are certain kinds of stress, or specific levels of different types of stress, usually beneficial? Are others usually harmful? Do the two—good and bad stresses—have broadly defining characteristics?

- Which aspects of cellular stress resistance are most closely tied to healthspan and longevity in animal models?

- Are aspects of the stress response (for example, pathways switched on by oxidative stress) typically preserved or enhanced by interventions known to enhance longevity in animals?

- Can interventions beneficially induce or enhance the stress response in animals to promote healthspan and longevity?

- Are there sex-specific aspects of the stress response that contribute to male-versus-female differences in healthspan and longevity?

- Is the stress resistance of particular types of cells, such as fibroblasts in the skin, predictive of future risks of diseases of aging in humans? Can measurements of stress resistance in human cells that are readily obtainable, such as white blood cells and fibroblasts, be used to predict healthspan and longevity?

- Can interventions, such as dietary components or pharmacological agents, activate human stress responses in a way that broadly lowers risk of diseases of aging and increases healthspan?

Tools & Models

Gerontologists' toolboxes have been greatly expanded by the same advances that have brought us bioengineered medicines and genetic tests that help oncologists select the best drugs to deploy against certain cancers. Applying the tools to study aging remains a work in progress, however, due both to the costs of new technologies and to the inevitable learning curves for mastering and harnessing them. Meanwhile, new animal models are being developed, such as the incredibly durable naked mole-rat, which promise profound insights into the aging process and how it might be altered to increase healthy life.

<u>The need for new tools & models</u>

- Sequence the genomes of healthy centenarians in order to provide a better control for identifying selected disease genotypes, and to uncover what makes centenarian genotypes different from those of normal individuals.

- Expand the NIA's Interventions Testing Program in order to discover classes of compounds capable of extending the healthspan and lifespan of laboratory mice.

- Identify elements of late-life dysfunction in invertebrate models that are amenable to genetic analysis and are good proxies for age-related dysfunctions in humans—such as age-related memory deficits and cardiac function decline.

- Test novel antioxidant compounds targeted to mitochondria (sources of cell energy) in mouse models. These compounds have promise for ameliorating a common form of congestive heart failure.

- Develop novel animal models of spontaneous, age-related neurodegeneration—perhaps in certain breeds of dogs—that are more reminiscent of Alzheimer's and other human brain diseases than current animal models of such diseases.

- Investigate the mechanisms underlying resistance to diseases of aging in novel animal models, such as long-lived rodents that appear to be extraordinarily resistant to cancer.

- Assemble data on patterns of age-related diseases in marmosets—small, relatively short-lived primates that are more closely related to humans than most animals used in aging research—to facilitate their use in studies on the biology of aging, and, in the longer term, testing of candidate interventions to avert or delay age-related diseases.

- Expand "comparative gerontology" research to define the genetic basis for marked variations in healthspan and lifespan among relatively closely related species, such as chimpanzees and humans.

- Investigate candidate drugs for extending healthspan and longevity in dogs via a broad-based initiative involving gerontologists, veterinarians, animal-health companies, nonprofit groups, and individual dog owners.

- Identify human gene variants and other prognostic factors that can be assessed in middle aged people to identify specific variants of genes and environmental factors that characterize "elite agers"—people who are likely to reach advanced ages in remarkably good health.

- Elucidate the powerful ability of some simple animals to regenerate injured tissues. Such knowledge is likely applicable to the emerging field of regenerative medicine.

II.) Achieving the Grand Challenge Goal

While there has been great excitement surrounding the progress in aging research, a large gap remains between promising basic research and healthcare applications, and closing that gap will require considerable focus and investment. The field would benefit greatly from the formation of a coordinating committee on aging within the NIH that could improve the quality and pace of research that advances the understanding of aging, its impact on age-related diseases, and the development of interventions to extend human healthspan. In addition to the National Institute on Aging (NIA), the coordinating committee would be most effective if it also included the National Human Genome Research Institute and representatives from the major-disease focused institutes that have some role in aging research such as the National Institute of Neurological Disorders and Stroke (NINDS), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Eye Institute (NEI), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Cancer Institute (NCI). An even broader interagency committee composed of various agencies within the Department of Health and Human Services could further speed the process of turning this research into healthcare advances.

An increase in funding for aging research is also urgently needed to enable scientists to capitalize on the field's recent exciting discoveries. Congressional appropriations to fund the efforts that grow out of the work of the coordinating committee would allow for major advances across diseases. Advocates for age-related diseases like Alzheimer's disease and cancer have called for Congressional appropriations of $2 billion annually in order to achieve major breakthroughs in treating and curing those diseases. Thus, a similar goal for aging research on the basic underpinnings of aging over the next 3 to 10 years seems modest considering its great potential to lower overall

disease risk (including Alzheimer's, cancer, and more) and add healthy years to life. We would recommend the establishment of a Blueprint for Geroscience at the NIH, modeled off of the successful model of a Blueprint for Neuroscience for achieving this goal.

The payoffs from focused attention and investment would be large and lasting. Research leading the way to therapies that delay aging would lessen our healthcare system's dependence on the relatively inefficient strategy of trying to redress diseases of aging one at a time, often after it is too late for meaningful benefit. They would also address the fact that while advances in lowering mortality from heart attack and stroke have dramatically increased life expectancy, they have left us vulnerable to other age-related diseases and disorders that develop in parallel, such as Alzheimer's disease, diabetes, and frailty. Properly focused and funded research could benefit millions of people by adding active, healthy, and productive years to life. Furthermore, the research will provide insights into the causes of and strategies for reducing the periods of disability that generally occur at the end of life.

We believe that the field of aging research is poised to make transformational gains in the near future. We hope that the recommendations for a grand challenge to slow aging as a means of preventing multiple chronic age-related disease at once, and the steps outlined to achieve this grand challenge goal, are included by OSTP in the Administration's Bioeconomy Blueprint. Few, if any, areas offer greater potential returns for public health. If you have any questions or would like additional information, please do not hesitate to contact me or Cynthia Bens the Alliance's Director of Public Policy at (202) 293-2856.

Sincerely,

Daniel P. Perry
President & CEO

Submitted electronically to: bioeconomy@ostp.gov

125th aps ANNIVERSARY 1887–2012

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December 5, 2011

Response to Office of Science and Technology Policy
Request for Information: Building a 21st Century Bioeconomy
BIOECONOMY@OSTP.GOV

The American Physiological Society (APS) appreciates the opportunity to comment on federal efforts to foster innovative research. The APS is a professional society dedicated to fostering research and education as well as the dissemination of scientific knowledge concerning how the organs and systems of the body function. The Society was founded in 1887 and now has over 10,000 member physiologists who conduct research at colleges, universities, medical schools, and other public and private research institutions across the U.S. We offer these comments on behalf of our members. Please note that we did not address each of the 17 questions posed in the request for information.

(1) *Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.*

Years of research into the molecular components of biological systems have provided the raw materials for understanding the functions of cells, tissues, organ systems, intact organisms and even whole populations. However, despite tremendous gains in biomedical research there remains a need to integrate what we know about biology on the molecular and cellular levels with the function of organisms in all their physiological complexity. Doing so will lead to a better understanding of human health and disease, and facilitate the development of new treatments and prevention strategies. The scientific community is poised to move forward into these exciting new areas, but doing so will require funding support and recognition within funding agencies of how this work is critical to translational research. Federal agencies could further these translational goals through requests for applications and other funding mechanisms. Importantly, additional support much greater than currently available will be necessary to speed progress and take advantage of scientific opportunities.

Another major challenge facing biomedical researchers is the integration and analysis of multi-dimensional data sets. Technologies developed in the last two decades have generated large amounts of different types of data. In order to take full advantage of this growing resource, the scientific community needs researchers with the necessary skills to harness the data and trained in both the biomedical and computer sciences. Research-intensive engineering and computer science universities should be encouraged to collaborate with health science partners to train researchers for work in this area.

(2) *Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?*

Trying to identify "high impact research and innovation opportunities" may be counterproductive because it is difficult to identify such research in its early stages. It can often take years for the impact of a research discovery to become apparent. A narrow focus on identifying and funding high-impact research may not be an effective use of resources and could result in missed opportunities to fund research that may have unanticipated long-term impacts.

(3) *What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative[1])?*

The National Institutes of Health (NIH) is trying to focus on translational research with the goal of accelerating the application of basic research findings. Basic physiological research has an important role to play in this process through target validation, efficacy testing and the identification of biomarkers. For example, one area of emphasis in the plan to streamline translational research is using high throughput techniques to identify target molecules and compounds that can potentially point the way to a new drug. This approach will require further research to validate the effect of these compounds in physiological systems.

Physiologists can place data generated from high throughput techniques into the context of physiological systems and aid in the development of preclinical models. Although working with animal models is expensive, time-consuming, and challenging, this work remains an important safeguard in the drug development process. We can maximize the benefit of high throughput technologies by continually improving validation models whether they are *in vivo, in vitro,* or *in silico*.

To solve large scale problems, collaborations will be necessary to bring together scientists with the appropriate expertise. One example of fostering collaboration to address major challenges comes from the National Institute of Allergy and Infectious Disease, which is funding three major HIV/AIDS research ventures targeting eradication of the disease, each characterized by investigators at several institutions and crossing traditional boundaries. This effort, the Martin Delaney Collaboratory, aims to accelerate progress toward a cure for AIDS by facilitating research partnerships among government, academia and industry.

(4) *The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?*

As referenced in our answer to question #1, we should build on the wealth of molecular data, including genome sequences that have been generated. Physiologists are particularly well positioned to advance understanding of gene function in the context of physiological systems. This should be made a priority.

(5) *What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.*

The APS supports efforts to promote a better exchange of ideas and materials between researchers in academia and industry. As part of the NIH effort to advance translational sciences, the agency has been trying to develop agreements giving academic scientists access to unused or underutilized compounds. These are Intellectual Property (IP)-protected compounds that pharmaceutical companies may have developed for one purpose that could serve another or else the company decided not to pursue because it did not work as expected or toxicity problems arose. The Drug Rescue and Repurposing initiative is part of the Chemical Genomics Center Pharmaceutical Collection. This effort is designed to determine whether the compounds that have been approved for market and the thousands of compounds that never made it to market might be useful for diseases other than their intended purpose. The bio-industry and universities could play a big part in bioinformatics, development of new high-throughput screens, and safety and efficacy assessment of these compounds. There are numerous issues still to be worked out, including how to deal with IP issues.

The APS also recommends that the government look carefully at financial conflict of interest policies to ensure that they are not unnecessarily inhibiting productive scientific relationships between federally-funded researchers and their colleagues in industry. It may be advantageous to look for ways to incentivize research partnerships between sectors in the “pre-IP” space.

(6) *What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs[2] would help accelerate commercialization of federally-funded bioeconomy-related research?*

The APS recommends that SBIR and STTR programs be evaluated to assess whether they are meeting the goal of increased commercialization of research discoveries.

(7) *What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?*
Are there data and/or drugs sitting in government labs, which have not been made publically available? The pressure to publish is less if you are in the NIH intramural community and as such there may be valuable data that in inaccessible to the broader community. Could we suggest some sort of data sharing for unpublished data from government research labs?

The APS recommends encouraging interactions between intramural and extramural scientists by incentivizing intramural scientists.

(9) *The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?*

This topic was recently addressed in a request for information (RFI) from the NIH (NOT-OD-11-106). The comments below were submitted on behalf of the APS in response to that RFI:

> One approach as outlined below, would be to change the nature of the PhD training process, which could provide added flexibility and will be more readily adaptable to shifts in demand for qualified biomedical researchers.
>
> Consideration should also be given to ensuring balance between disciplines. Some fields of research may have too many students entering training programs for the available number of post-graduate career opportunities, while others have too few students entering the pipeline.
>
> *Characteristics of PhD training in biomedical research*
>
> Graduate training (at the pre- and post-doctoral levels) should be focused on trainees developing the skills and knowledge required to solve our nation's biomedical and health problems and become productive members of the biomedical workforce. Trainees should be provided with career development resources designed to match the needs of the marketplace.
>
> Currently PhD training programs do an excellent job of preparing students for careers in academic science. But biomedicine needs a broader diversity of professionals to be successful, and PhD programs are not designed to prepare students for these careers. One way to achieve this goal would be to alter pre-doctoral graduate training such that the first two years provide a broad base of knowledge and skills, including program curriculum, research experience and career development. Career development should include the skills necessary to run a successful research program including business skills, project and lab management, as well as resources to prepare students for careers in fields beyond academic bench research. This two year training program may culminate in the award of a Master of Science degree, followed by entry into a PhD program. Given the prior two years of training we would anticipate that the PhD program would be more focused on research with reduced emphasis on course work.
>
> Clearly, new mechanisms of support will need to be developed for the Master's degree portion of training, including scholarships, loans and teaching assistantships; such funding mechanisms will be especially important to ensure that under served minority groups continue to enter the biomedical research work force. Once a student moves to the PhD program we would anticipate that federal support would be available from training grants and other similar mechanisms.
>
> We anticipate that this approach will provide graduate students an additional set of basic skills to expand their career opportunities, as well as result in a more flexible pipeline for biomedical research by effectively increasing the scientific workforce while at the same time providing for increased career opportunities.

(10) *What roles should community colleges play in training the bioeconomy workforce of the future?*

The APS recommends improving the quality of science education at community colleges and aligning science curricula with the needs of four year colleges and universities. This will allow community college students to make a fluid transition to programs in biological, biomedical and bioengineering programs.

There are a large number of qualified individuals graduating from high school who cannot afford the costs of a four year education at leading colleges and universities. Thus, by creating cutting edge science programs at the community college level, which are inherently more affordable compared to the four-year college and university setting, it will be possible to enable more qualified individuals to move through the pipe line to meet future needs for scientists and physicians. This system is in place in the state of California where certain community colleges have been aligned with the University of California campuses to create such a feeder system.

(11) *What role should the private sector play in training future bioeconomy scientists and engineers?*

As referenced in our response to question # 9, the APS supports the idea of offering career training to pre-doctoral students. To ensure that the next generation of scientists has the skills to meet the needs of the workplace, it would be advantageous to encourage the development of training programs that involve partnerships between industry and academia. It is especially important for graduate students and faculty to be informed of what industry is looking for in science. The drive for translational research as well as academia's growing involvement in the drug discovery process requires that university scientists gain a solid understanding of the important questions that need to be addressed, for example, target validation, target engagement, develop ability and selectivity of drug candidates, biomarkers, potential companion diagnostics etc.

Many graduate programs bring in scientists from the pharmaceutical industry to speak with students about the drug discovery process, working in industry and interviewing for industry jobs. These efforts should be encouraged and expanded.

(12) *What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?*

Please see our response to question #11.

(13) *What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.*

Currently federal public health service (PHS) regulations require review of animal protocols every three years. However, most research grants provide support for four years. Harmonizing the review cycles for federal grants and animal research protocols would substantially reduce regulatory burden and free up resources at the level of the individual investigator, institutional administration and federal agencies.

(14) *What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)*

Federally-funded researchers are typically subject to regulatory requirements from more than one federal agency. It would be advantageous to harmonize the regulations between agencies to reduce burden on individual investigators.

In addition, oversight agencies such as the USDA should take a constructive approach with respect to enforcing the Animal Welfare Act. Research institutions monitor their own compliance with the AWA through an Institutional Animal Care and Use Committee (IACUC) that reports to a designated Institutional Official. This often results in the prompt identification and correction of problems. We strongly urge that the USDA avoid taking a punitive stance when an IACUC does its job. In other words, a self-identified and self-corrected problem that is documented by the institution should not result in a USDA citation unless it represents serious and continuing noncompliance.

(17) *What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?*

NIH could and should facilitate cross-institutional collaborations. It can be very difficult to collaborate with research partners at other institutions, when jurisdictional responsibilities between regulatory committees in different institutions are not clear. It is redundant and wasteful for committees at two institutions to review all aspects of collaborative projects.

In conclusion, we would like to reiterate that maintaining a first rate biomedical research enterprise now and in the future is critical to the health and welfare of Americans and economic competitiveness. Thank you for considering our comments.

Sincerely,

Joey P. Granger, Ph.D.
President
American Physiological Society

Society for Neuroscience
Response to the Office of Science and Technology Policy
Request for Information: Building a 21st Century Bioeconomy

1) Identify one or more "grand challenges" for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

Progress in neuroscience, and for related neurological diseases and disorders, requires an emphasis on both fundamental and disease-oriented research, as well as the unwavering commitment of national will, substantial appropriate funding of leading-edge scientific research, and the application of innovative policies. If the United States makes these commitments, it can advance scientific understanding and treatments for diseases and disorders that cost more than $100 billion annually in the U.S. alone and affect nearly one billion families worldwide. Those numbers are expected to grow significantly with aging and growing populations around the world. In fact, investing in neuroscience research is one the most important deficit reduction efforts nations can undertake. Scientific and medical advances have allowed people to live longer. Without a means of treating or preventing debilitating diseases of our aging population, we will be facing an economic disaster. Basic research will provide the insights that enable disease-oriented research to be effective and lead to treatments. The question is not whether we can afford to invest in neuroscience; it is whether we can afford *not* to.

Investing in scientific research also contributes to economic revitalization and global competitiveness. In the U.S., medical research is one critical element in a national effort to build and maintain a high-technology, high-wage economy. A recent report by United for Medical Research, entitled *An Economic Engine NIH Research, Employment and the Future of the Medical Innovation Sector*, noted that in 2010, investments in NIH resulted in the creation of roughly 485,000 jobs and produced nearly $70 billion in economic activity.

Recently, SfN has launched an initiative to identify major scientific opportunities in the field and then evaluate near-term and long-range steps SfN and others in neuroscience leadership could take to catalyze and support those opportunities. In coming months, SfN looks forward to working on this initiative and sharing the outcomes with the White House Office of Science Technology and Policy (OSTP) as well as other science and public policy leaders. In the meantime, we appreciate the opportunity to respond to this "Request for Information" on the Bioeconomy Blueprint, and, where appropriate, we refer OSTP to important thinking already underway in the community on these subjects.

Specifically, in May 2011, One Mind for Research, an effort initiated by former Rep. Patrick Kennedy, was launched with a goal to energize neuroscience research and development throughout the next decade. A major outcome of that meeting was the *10-Year Plan for Neuroscience* ("Plan"), which was developed under the leadership of neurobiologist and then-Harvard University Provost Steven Hyman and in partnership with a committee of leading neuroscientists — in industry, academia and government — organized through SfN. The 10-year plan, designed as a living document, outlined major emerging opportunities in brain research. These are precisely the type of far-reaching, high-impact focal points that the Society believes should inform the Bioeconomy Blueprint and that we encourage OSTP and the nation to consider. An overview of the Plan's priorities follows; details, including key goals and opportunities within each priority, can be found at www.1mind4research.org.

A. Genetics

Genetics has revolutionized biological approaches to many neurodegenerative disorders, including Huntington's disease, Parkinson's disease, heritable ataxias, Alzheimer's disease, and frontotemporal dementia. Identification of genetic variation associated with disease is beginning to provide critical clues to what goes wrong in the brain in many devastating neuropsychiatric disorders that are influenced by a large number of different genes, including forms of cognitive disability, autism, schizophrenia, and bipolar disorder. Indeed, whole exome and whole genome sequencing will tell us a great deal about human biology and result in a greater understanding of human health and disease.

B. Epigenetics

Epigenetics is the study of an important set of mechanisms that contribute to deciding which genes are expressed. While the study of how genes are activated or silenced is decades old, there has been a new burst of excitement about epigenetic mechanisms of gene regulation because these could explain very long-lived changes in brain function that result from environmental influences. Some of these changes in gene expression may exert long-lived effects on physiology and behavior and thus have great importance to brain health and to treatment development. Drugs that might influence epigenetic regulation of gene expression are already being investigated for the treatment of memory disorders and depression.

C. The Connectome: The "Wiring Diagram of Nervous Systems"

Given the enormous number of neurons in the human brain, and the even greater number of synapses it has been a challenge to develop a complete and accurate wiring diagram. Exciting new tools have given birth to a field known as connectomics. A complete human connectome represents a highly ambitious goal that could not have been envisioned by anatomists looking at brain slices under a microscope. As connectomics progresses, however, it should yield significant insights into human brain disorders, most obviously those that are thought to result from developmental abnormalities in brain circuits, ranging from learning disorders to autism to schizophrenia.

D. Neural Stem Cells

Improving understanding of the development, functions, and vulnerabilities to degeneration and damage of distinct neuron types will result in new and better approaches to the prevention and treatment of human nervous system disorders. Neural cells derived from patient-derived stem cells offer the opportunity to test new drugs and treatments in appropriate cell environments.

E. "Systems Biology" and beyond: Putting the nervous system together again

Over the last decade, beginning with research on cells simpler than neurons, a group of conceptual approaches have emerged under the banner of "systems biology." Examples are beginning to emerge in which sequence variation in different parts of the genome point toward shared pathogenic mechanisms in some heterogeneous disorders, such as autism. Modern methods and computational analysis have enabled scientists to look not only at specific parts of living organisms but see how these parts—genes, proteins, cells and tissues—interact together. A systems approach is yielding new insights that cannot be revealed by looking at individual components and it will ultimately allow for new views of human biology that is mechanistic in its scope.

F. New Forms of Scientific Organization

The generation of ambitious global data sets for neuroscience requires different systems of organization than the traditional small academic research lab. The resulting data sets, and in many cases, computational tools, produce substantial benefits for the entire field of neuroscience, including small academic laboratories engaged in hypothesis-driven research. A cornerstone of progress in genomics that became a critical cultural norm within the human genome project is the rapid and open sharing both of data sets and of computational tools. Beyond the genomics community, the Alzheimer's Disease Neuroimaging Initiative (ADNI), for example, is a partnership that involves government (NIH), industry, and several foundations. These examples illustrate the need for academic laboratories engaged in hypothesis-driven science and point to the emergence of a new, richer ecosystem in which academic labs are enhanced by collaborations with nontraditional research organizations, government, and industry.

2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

Over the past year, the SfN Council has begun an effort, which is still in its early development, to evaluate the knowledge base, research infrastructure, and support mechanisms that are essential to address for the future of neuroscience. The Council agrees that making choices about scientific priorities, the tools most important to develop, and the mechanisms to support real innovation will be central to this effort. In the view of the SfN's leadership, the evaluation of core priorities will begin with a commitment to the following:

- **Identifying critical research areas and gaps** in scientific knowledge.

- **Supporting the most creative science**, both emerging topics and innovative approaches. It is important that we build upon the successes of the current grant review system to allow for more high-risk and high-payoff scientific endeavors.
- **Ensuring outstanding young scientists are inspired and motivated** to continue in research and are free to take risks and innovate.
- **Establishing new partnerships across disciplines** that are currently far apart and disconnected.
- **Enriching the scientific infrastructure** by developing new cutting-edge technologies to explore how genes, cells, neural networks and systems operate in the healthy brain and how normal processes are altered in the diseased or injured brain.
- **Developing and supporting coordinating mechanisms**, helping researchers collaborate, share resources, and exchange ideas and information among different institutions both nationally and internationally.
- **Removing barriers to new treatments** through radically rethinking partnerships between academic laboratories, the pharmaceutical industry, and health care providers.
- **Ensuring a sustained and aggressive national research funding commitment** that enables progress on all of the above. The grant system employed by NIH emphasizing investigator-initiated individual grants (i.e. RO1s) and collaborative Program Project grants (i.e. PO1s) has proven to be highly successful in providing new insights to basic biomedical problems. These funding mechanisms should be given additional support.

3) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

While high throughput approaches are critical to enhancing and advancing the field, the insights and advances that will lead to new treatments for a myriad of human disorders will come not only through these technologies but also through fundamentally different ways: some from research targeted to solve a particular disease, and some via totally unexpected routes and serendipity.

Now more than ever, it is important to continue funding for research that is technology driven while maintaining the vibrancy of investigator-driven research and remaining attentive to the importance of research at many levels — from the most basic to translational. Progress in science depends on imaginative, curiosity-driven research that makes leaps in ways no one could have anticipated. When resources are limited, balancing support for high-risk high-payoff ideas with disease-driven translational research presents a huge challenge—it is easy to see why the latter is important, yet ultimately both kinds of research have the potential to contribute to the development of life changing therapies and cures for different diseases.

4) The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

There are potentially many ways the broader neuroscience community would recommend leveraging genetic knowledge and its relevance for protein function. As an example, one important advance would be to emphasize the biochemical and functional analysis of unknown proteins, which will reveal new insights into biological pathways and disease. An important problem is an understanding of membrane proteins, a critical problem in neuroscience research. Another issue is finding out the normal function of proteins implicated in neurological diseases. This includes amyloid precursor protein (Alzheimer's disease), alpha-synuclein (Parkinson's disease) and huntingtin protein (Huntington's disease), whose functions are not understood at all. This will require the concerted efforts from cell biologists, X-ray crystallographers, biochemists, pharmacologists, computational scientists.

There are already efforts to obtain whole genome sequences from individuals suffering from brain tumors or autism. Interpretation of this massive amount of data will require new algorithms and sophisticated computational analysis.

5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

In recent years, the global neuroscience community has seen an accelerated and large-scale retreat from pharmaceutical innovation and investment in the CNS space. With notable exceptions, most of the major pharmaceutical manufacturers have decreased investment in this area significantly, with most companies launching large-scale layoffs and retrenching to more predictable and lucrative research lines. In doing so, research companies have expressed substantial concern about opportunities in the space, and have noted the lack of viable new therapeutic targets for brain diseases and disorders. They note the high cost of work to validate drug targets, as well as high failure rates and the likelihood that failure occurs late in clinical trials.

Given the innovation underway in neuroscience, and the scope and cost of neurological diseases and disorders, this is a situation that calls for swift and significant evaluation of potential interventions. In the current environment, pharmaceutical industry leaders are looking for ways of "de-risking" potential targets, at a presumed cost in the billions of dollars – resources that are not within sight in the current severely-constrained federal budget environment.

There is wide-but-early dialogue in the broader neuroscience community about innovative approaches that could help address this situation constructively, but these are not yet ripe for final decision-making. The Society believes that the White House and OSTP could make a

major contributing effort to advance translation from lab to commercial markets by facilitating dialogue between key actors. Key questions to foster dialogue include:

- **Pharmaceutical industry leadership**: How might the industry expand support for basic and early translational research, as well as other "de-risking" work that used to be paid for and conducted within corporate research structures? Pharmaceutical companies are presently concentrating research and development in "clusters" near university research centers. Will the proximity to academic talent pools increase the chance of more innovation?
- **Academic institution leadership**: How might academic institutions help affiliated researchers and institutions balance shared demands of research, teaching, and entrepreneurial business development? How can institutions facilitate the need to break down silos and barriers between departments that are carrying out similar research goals?
- **National Institutes of Health leadership**: What is the NIH capacity (and are they well positioned) to fund expansion of translational science while maintaining support for discovery research that stokes the long-term pipeline of medical research?
- **Basic scientists and clinicians:** What can scientists do to enhance the research community's knowledge about translational opportunity – how to recognize it, nurture it, and engage with it? Translational research not only depends upon "bench to bedside," but also requires clinicians to participate in basic research and basic researchers to better understand clinical needs. MD/PhD programs are one way to facilitate this exchange; are there ways to foster and train more—and more successful—"physician-scientists?" The idea is to do more to instill PhD's with an understanding of the clinical relevance of basic science and to foster MD participation in the science behind medicine.
- **Emphasizing training to young students in science, math and technology.** It is now evident that a majority of American students planning science and engineering majors are switching to other careers, due to the length of training, economic concerns and lack of new independent positions. Also, test scores indicate that American students are falling behind students in many countries. What can be done to offset this trend, such as a concerted effort to encourage and expose students at a young age to the possibilities and excitement of scientific discovery? For example, NSF has supported summer high school programs in basic research. How can we continue and expand these programs to expose students at an early age to science programs?

6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?

SfN is enthusiastic about fast-tracking commercialization of research and would encourage OSTP to catalyze dialogue with the private sector and their scientific advisory boards about the opportunities across the CNS space. Presently, many scientists would argue that not enough high quality research proposals are submitted for SBIR funding. There is a need to identify outstanding science that is connected to business, and that could mean that

incentivizing more communication and coordination between the scientific and business communities would be very productive and cost-effective way of accelerating commercialization—without getting the federal government into activities where the strengths of the private sector might be better leveraged. One example could be an effort to match clusters of academic research to small business in communities beyond the established biotech research centers, including those in Boston, the San Francisco Bay Area, San Diego, and outside Philadelphia.

7) What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

The Society for Neuroscience continues to evaluate ways the field can leverage data to facilitate neuroscience innovation and discovery. For instance, SfN was an originating organizer of the Neuroscience Database Gateway, an early predecessor of what has today become the Neuroscience Informatics Framework developed under the leadership of the National Institutes of Health to "promote resource discoverability and integration…to connect neuroscientists and biomedical researchers to available resources." Additionally, SfN has been a supporter of efforts to leverage scientific publishing to support discovery. It strives to do so while balancing the need to protect healthy competitive forces that propel science, and preserve a scientific publishing enterprise that provides significant value through intensive peer review systems and well developed dissemination mechanisms.

In the recent past, SfN explored interest expressed by some neuroscientists to facilitate searching and mining of text and data in the neuroscience literature, in supplementary data, and in independent neuroscience databases. This could provide access to a rich array of information and help accelerate the pace of discovery through more effective communication. One past working group discussed the importance of capturing metadata – key descriptors of experimental data and design – to enhance searching for articles and scientific content of interest. Another working group explored ways to improve the linkages between journal articles and data repositories. OSTP might facilitate a dialogue with scientists and publishers, there might be a ways in which data sharing could be enhanced by improving links between online articles and databases and by encouraging authors to submit their own data to a database.

SfN would encourage continued recognition and engagement by the scientific community in pursuit of effective data sharing activities, both in terms of databases and appropriate access to publication data – doing so would recognizing the dynamic nature of science, the role of the scientific publishing community, and the latter's growing interface with neuroinformatics as a discipline.

8) What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

Orphan drugs and rare diseases (Spinal Muscular Dystrophy, Rett's syndrome, Huntington's disease etc.) could be looked at more carefully by the private sector, as they will be relevant to many disorders that affect a much larger number of people in the population. It is very likely the information gained from rare diseases will be directly applicable to more common

disorders. Pharmaceutical companies could be incentivized to study rare diseases, as they related to prevalent neurological disorders such as stroke, autism, Alzheimer's and Parkinson's disease.

9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Training grants and graduate programs are geared towards producing PhD scientists best suited for conventional faculty positions, with few alternative or intermediate options. There is also an inherent conflict of interest between the very act of training and the way that academic principal investigators depend on students and fellows to execute NIH-funded work. One area worth considering is whether we should be training students and fellows differently by preparing them for other kinds of professional research positions (not only PhDs, but also Masters level and other degrees as well) that are distinct from tenure stream faculty appointments. However, we must be careful not to push too far toward a system of larger professionally staffed labs. Such a system could result in a more stifling vertical scientific hierarchy and would raise the risk of losing our most energetic, early-stage faculty, who rely heavily on student workers. These issues illustrate the complexity inherent in reshaping training strategies or numbers of trainees, and underscore the need to proceed slowly, thoughtfully and deliberately in any effort to restructure the biomedical workforce. Finally, we cannot address workforce issues without acknowledging the need for diversity -- diversity of experience, diversity of intellectual backgrounds, and diversity of perspective. The more uniquely each scientist thinks the richer and more imaginative our discoveries will be. Thus, in addition to concerns about younger researchers and basic science, our commitment to diversity must include attention to fostering the development and career advancement opportunities for women in neuroscience and for under-represented minorities. A recent internal NIH audit highlighted some of these concerns when it found that black scientists are significantly less likely than white researchers to win grants from the NIH (Ginther et al, 2011).

10) What roles should community colleges play in training the bioeconomy workforce of the future?

Community colleges could play a vital role in technical training in the research technologies of the future. They include mass spectrometry, medical imaging, small molecule screening and DNA sequencing and bioinformatics. Students at community colleges could be encouraged to seek new opportunities and learn a new range of skills and abilities. An additional role for community colleges is to recognize "diamonds in the rough" and prepare them for scientific careers.

11) What role should the private sector play in training future bioeconomy scientists and engineers?

Fellowships, internships and prizes could be provided to stimulate young people to enter science and engineering. Partnerships with universities and colleges — in which students are given the opportunity to be exposed to research efforts in pharmaceutical companies, foundations working to support scientific research, and scientific journalism and

communication that builds awareness of scientific achievement — are needed to promote future bioeconomy scientists and engineers.

12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

There is growing concern in the global neuroscience community, including in the U.S., about the increasing burden of animal research regulation. Scientific and health advances are made possible within a regulatory system involving federal, state, institutional, and community review that protects animal welfare. Scientists who do animal research understand that they must use animals sensitively, appropriately, and humanely, using as few animals and as many alternative techniques as possible to achieve reliable results. Nonetheless, there are some avenues of inquiry for which computer models, cell culture, and noninvasive techniques may never replace the use of live animals specifically bred for research purposes.

Many in the scientific community are concerned that regulatory requirements are beginning to supplant rigorous scientific questions as the starting point for discovery. That is, the scientific merits of an inquiry (driven by the desire to advance science or improve health outcomes) are increasingly presumed to be secondary to needs of regulatory frameworks arbitrarily established outside the scientific setting.

For example, the scientific community is concerned about the possible adoption by the NIH Office of Laboratory Animal Welfare of the *Eighth Edition of the Guide for the Care and Use of Laboratory Animal* (*Guide*) in its current form. Neuroscientists take seriously the ethical considerations and strict protocols necessary to engage in responsible animal research. Unfortunately, the proposed *Guide* creates a significant expansion of explicit requirements and de-facto required "guidance," as well as a large number of revisions that appear to lack sufficient scientific justification. There is growing concern that the *Guide* will result in significantly increased regulatory costs and time burdens for researchers with little demonstrated benefit. In fact, the National Association for Biomedical Research (NABR) submitted comment to the NIH regarding adoption of the *Guide* and reported: "Based on preliminary assessments by many of [NABR's] members, one of the new provisions included in the 2011 *Guide* would impose increased costs on PHS-assured institutions of more than $100 million annually, which would materially alter the budgetary impact of NIH grants."

Thus, the *Guide* is likely to slow medical research effectiveness and result in no meaningful benefit for animal subjects. These are outcomes that both the research community and governmental bodies should reject as they are counterproductive to the charge we have been given—to advance science and improve health.

14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

While SfN's policy focus is primarily on research funding and priorities, we would note that the Food and Drug Administration (FDA) process could be ripe for evaluation and could likely be improved with regard to the time taken to approve new drugs and medical devices. There are many delays, and OSTP could evaluate whether undue, excessive paperwork and bureaucracy is hampering its effectiveness. As there are always difficult hurdles regarding safety, side effects and the need for new drugs, the administration could work with the FDA and key community stakeholders to identify ways to ensure the public is better informed about the positive and negative consequences of new treatments.

15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

Biotechnology companies spend over $50 billion a year on research and development, but the number of new drugs that are produced is exceedingly low (20-25). Clearly, there is a disconnect between the costs of development and the identification of successful treatments. In addition to SfN's strong recommendation for discussion among multiple actors to enhance the discovery-to-treatment pipeline (see response to question #5), an additional option would be for OSTP to explore how the clinical trial system could be streamlined and whether a new electronic data management system that takes into account personalized medicine could facilitate faster, and more efficient, application of medical advances for individual benefit.

Additionally, there is no doubt that the NIH has been very successful at funding basic research and providing the basis for much of the translational efforts of the pharmaceutical industry. SfN would encourage very close evaluation, including input from a wide variety of stakeholders, to determine whether or how NIH could be productively involved in the development of commercial products. Improvements in the drug approval process by the FDA will more likely move and accelerate the generation of new pharmaceuticals.

16) What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

SfN believes there may be global models that could inform U.S. strategies in this area. For example, in June 2011, the Canadian federal government allocated $100 million to establish the Canada Brain Research Fund "to support the very best Canadian neuroscience," to be matched by $100 million in private sources.

Brain Canada, a non-profit organization that will administer the funds, reports the program will "increase funding in support of brain research of the highest caliber and impact; accelerate the rates of discovery and the translation of research discoveries into benefits for all Canadians; and stimulate collaborations" to enhance research effectiveness. "It will select funding recipients through an open competition and rigorous … peer review."

Grant funding, in particular, is designed to "accelerate 'transformative' research to discovery and to the development of new treatments and therapies for neurological and psychiatric diseases. Brain Canada will achieve this by funding teams of investigators from various disciplines and institutions that have the best chance of producing rapid progress in understanding and treating brain diseases. The funding criteria [are] excellence and novel and paradigm-shifting ideas as assessed by US and European reviewers, emphasizing discovery research with findings applicable to multiple neurological and psychiatric conditions."

SfN would encourage OSTP to explore this model, or potentially others, as part of the National Bioeconomy Blueprint effort. A central tenet of the program and one that could have application in the context of the bioeconomy is that grants could not be based on individual diseases, but on investigating commonalities among many conditions, including how the brain normally functions and how these functions are perturbed during disease. More information can be found at http://brainresearchcanada.org/.

17) What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

To: Office of Science and Technology Policy (BIOECONOMY@OSTP.GOV)

From: Teri Willey, Vice President for Technology and Business Development, Mount Sinai Medical Center, New York, NY

DATE: December 5, 2011

RE: Request for Information: Building A 21st Century Bioeconomy

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Thank you for soliciting feedback on this important issue. Below are my recommendations.

Encourage distribution of academic research results for the benefit of the public.

An extremely efficient means of translating basic research discoveries into commercially useful products can be achieved by directly combining the talents of academia and industry through alliances and partnerships. By working closely together through the entire continuum of R&D activities, from idea conception through market launch, such partnerships often provide the best hope of realizing real world benefit from strong academic research. Though many academic institutions have shied away from forming direct R&D alliances with industry out of concern that they would taint the integrity of academic research, more and more institutions are discovering that it is possible to maintain both a high level of academic integrity and productive R&D relationship through carefully crafted partnership and alliance relationships with industry. Indeed, Mount Sinai School of Medicine has embraced this as in integral part of their strategy to assure that the results of research and scholarly activities reach patients to address unmet needs. The federal government can play a critical role in solidifying and encouraging these critical activities, by providing direct support to institutions that embrace the alliance approach. While there are numerous ways in which government can help, there are two in particular for consideration:

1) **Increase the Private Use Exemption.** It would be extremely helpful if the federal government could provide greater clarity and flexibility with regard to the conditions governing research in buildings financed with tax free bonds. One of the major constraints on academic-industry collaborations are the restrictions placed on private use of tax exempt bond financed space, which often come into direct conflict with the goal of increasing such interactions. If industrial partnerships are to increase and flourish in the way envisaged by both the government and many academic institutions, the current allowance of 5% permitted use of said space (the safe harbor) will be an insurmountable obstacle to any appreciable expansion. We would recommend that the government give consideration to an increase in the safe harbor to 25% or above. This will have the double advantage of not only encouraging university-industry collaboration, but would be

a measure that can be taken at zero impact to the government's finances. Moreover, as long as a reasonable - but not excessively low - restriction remains, the government is still guarding against universities becoming out and out "for profit" entities. A real level of control can still being exerted without stifling necessary university - industry cooperation.

2) **Clarification re the America Invents Act.** Patent reform has been on the horizon for several years and has recently come to fruition, at least in part, through the Leahy-Smith America Invents Act (AIA) which was signed into law on Sept. 16, 2011. The Act makes sweeping changes to U.S. patent law and practice, including moving the United States towards a first-to-file system, redefining what constitutes prior art, expanding prior user rights as a defense to infringement, adding new options for challenging patents, revamping administrative proceedings at the USPTO, and modifying the USPTO fee structure. Because patent protection of certain academic research results is critical to creating an incentive to invest in the long term development of new therapies, it is important to understand how these changes in law will impact the ability of academic institutions to advance ideas which require intellectual property management and partnership with industry. Any changes in the law which cast uncertainly of the value of inventions may inhibit investment in early stage ideas. For example, with respect to question 8 in the RFI *what are the challenges associated with existing private-sector models for financing entrepreneurial bioeconomy firms?*, the new post-grant review procedure under the AIA allows anyone to assert that a patent should not have issued for an invention for any reason. The challenge does not need to be based on a prior patent or a prior publication. With the ambiguity of this new provision, will a company invest in a very new technology if the patent that issues for it can be challenged on ethical/quasi-legal grounds? Clarification of these provisions is needed as is their possible impact on financing bio innovation.

Mon 12/5/2011 4:29 PM

Response to RFI: Building A 21st Century Bioeconomy

INTRODUCTION

This set of recommendations is in response to the October 11, 2011 Request for Information (RFI) from the White House Office of Science and Technology Policy (OSTP) titled *Building a 21st Century Bioeconomy*. The stated purpose of the RFI is "to solicit input from all interested parties regarding recommendations for harnessing biological research innovations to meet national challenges in health, food, energy, and the environment while creating high-wage, high-skill jobs."

Biomedical Development Corporation is a small business located in San Antonio, TX.

We have recommendations on behalf of entrepreneurial companies located in areas where there is very little venture capital. Accordingly, these companies develop entrepreneurial approaches to research and development, manufacturing, and marketing.

Cognizant of the fiscal constraints facing the U.S. government at this time, **none of the following recommendations require new government spending.** At most they would require small shifts in funding from programs that are generally delivering less economic value. Furthermore, we believe that **most of these recommendations can be immediately implemented without the need for new legislation**. To the extent that any of these ideas require some legislative tweaks these would not require an appropriation and would likely garner bipartisan support.

RESPONSES TO SELECT REQUESTS FOR INFORMATION

What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both. (Q5)

The single greatest barrier to moving biological research discoveries from the lab to commercial markets is the low funding priority assigned by the National Institutes of Health (NIH) to technology transfer and translational research. Nearly all of the nearly $30 billion received by the NIH each year goes to hypothesis driven basic research by academics. While this research sometimes serves as a foundation for future clinical and commercial applications, NIH funding almost always ends long before private investment in the research can commence without undue risk. Furthermore, the amount of funding available for basic research significantly outweighs that available for the translation of early stage research into useful products.

What specific changes to Federal Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally funded bioeconomy related research? (Q6)

Adopt a more commercial and entrepreneurial (rather than academic or multi-national corporate) review process for the NIH SBIR program and recognize that all new jobs are important to our economy; not just "high wage, high skill jobs". Further, high wage, high skill jobs generate new opportunities and jobs across the economy. For example, commercializing a new technology often results in jobs across all segments including manufacturing, sales, marketing and distribution.

With regard to the current SBIR/STTR review process at NIH, we have several observations and suggestions.

<u>Observations:</u>

1. Reviewers generally approve "cutting edge science" and/or "something they would like to use in their labs" rather than "the best commercial opportunities."

2. Reviewers often view the selling of Intellectual Property (i.e., licensing patents) as an endgame instead of developing and selling products, which has a greater impact on the creation of jobs in the United States.
3. Reviewers typically do not appreciate that a small business can work a lot faster than a multinational corporation with its multi-layers of decision making, risk aversion and lack of entrepreneurial determination.
4. Reviewers do not take into account that unique, novel products are often difficult for multi-national corporations to integrate into their established structure.
5. Reviewers generally do not recognize the value of products that can be manufactured profitably in the United States and exported:

Suggestions:

1. Special consideration should be given to federally funded bioeconomy related research that can be commercialized in the near future in order to generate sales and jobs in the United States as quickly as possible.
2. Special consideration should be given to federally funded bioeconomy related research that will be converted to products that will be manufactured by the small companies in the United States.
3. Special consideration should be given to federally funded bioeconomy related research that small companies in the United States will market and sell in the United States and abroad.

Thank you for the opportunity to provide input.

--
Phyllis B. Siegel
C.E.O.
Biomedical Development Corporation
[redacted]

Association of University Technology Managers®
Advancing Discoveries for a Better World®

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Dec. 5, 2011

To Whom It May Concern:

On behalf of the Association of University Technology Managers (AUTM), I am pleased to respond to the Office of Science and Technology Policy Request for Information: Building a 21st Century Bioeconomy

AUTM is a nonprofit organization with an international membership of more than 3,000 technology managers and business executives. These members come from more than 300 universities, research institutions, teaching hospitals, government organizations and businesses.

We believe that academic technology transfer can help harness biological research innovations to meet national challenges in health, food, energy, and the environment while creating high-wage, high-skill jobs. To do so, we must provide adequate resources for technology development, reduce risk on the part of industry partners, free up capital for development of technologies and secure funding within the USPTO for the patent approval process. Therefore, we must:

Invest in the Building Blocks of American Innovation
The doubling of funding for basic research at universities and research hospitals will drive economic progress as demonstrated by a recent study published in the *New England Journal of Medicine*. This study demonstrates that over the last 40 years, 153 new FDA-approved drugs, vaccines or new indications for existing drugs were discovered through research carried out in public sector research institutions (PSRIs)[1]. The study also found that an increase of 1 percent in the funding of public basic research led to an increase of 1.8 percent in the number of successful applications for new molecular entities. The bottom line: Investment in basic research at universities and research hospitals pays off. Such funding is particularly critical as there is no movement by industry to dramatically increase its funding of early stage research as this is the highest risk research.

The federal government spends more than $50 billion on scientific research in academic institutions each year; the Bayh-Dole Act was intended to facilitate the transfer of useful inventions that resulted from this research to the private sector. However, Bayh-Dole made no explicit provision for funding the further development and transfer of these technologies. The framers of the Bayh-Dole Act anticipated that operating expenses for technology transfer would be included in the administrative component of each institution's indirect cost base. However, in the early 1990s these costs were capped at 26

[1] The Role of Public-Sector Research in the Discovery of Drugs and Vaccines, Ashley J. Stevens, D. Phil.; Jonathan J. Jensen, M.B.A.; Katrine Wyller, M.B.E.; Patrick C. Kilgore, B.S.; Sabarni Chatterjee, M.B.A., J.D.; Mark Rohrbaugh, PhD, J.D., The New England Journal of Medicine, vol. 364, February 10, 2011

percent. The result is that a significant portion of technology transfer costs at universities are generally not funded through administrative indirect costs.

Instead, academic institutions have had to provide their own funding for technology transfer activities. A recent study[2] shows that they spend only 0.59 percent of their research budgets on technology transfer, a seemingly disproportionate figure given the expectation for technology transfer offices.

The study found that for 84 percent of academic institutions in 2006, technology transfer represented a net cost to the institution, and that only 16 percent of technology transfer programs retained enough of the income they generated to cover all the costs of the function. As a consequence, many academic institutions under invest in their technology transfer function and therefore potentially promising technologies are not protected and transferred. Technology transfer should be valued and resourced properly, and each university should have the flexibility to fund technology transfer in whatever way best serves its mission.

Promote Market-Based Innovation

AUTM has worked with the higher education associations in negotiating the recent patent reform bill, the America Invents Act. We believe this Act will accelerate the process of patent approvals, and provide appropriate protection of university technologies so long as adequate funding remains under the control of the Patent Office.

The success of a startup company or small business often hinges on access to small amounts of capital. Making the Research and Experimentation Tax Credit permanent for these businesses will be a welcome relief as will the increased financial support in the Small Business Jobs Act, which the President signed into law last year.

Increase Opportunities for Collaboration with Universities by SBIR and STTR Awardees

In order to reduce the need of early stage small businesses to buy capital equipment and build facilities they cannot afford, we also recommend increasing the percentage of an SBIR and STTR award which may be subcontracted by an additional 20 percent so long as those funds are spent for renting laboratory equipment, test facilities, or prototyping facilities at universities, research hospitals, or government laboratories or for paying staff of those entities to operate that equipment or facilities. Such an increase is supportive of the President's initiative to increase access to Proof of Concept Centers in the US.

Catalyze Breakthroughs for National Priorities

Also encouraging is NIH's National Center for Advancing Translational Sciences (NCATS). It is clear the administration grasps the challenges of translating early stage technologies into usable products and services. Building a center focused on bridging this gap will offer numerous opportunities for technologies that otherwise may never be fully developed. AUTM has long been a supporter of more translational research funds and we look forward to seeing the results of NCATS.

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[2] How Are US Technology Transfer Offices Tasked And Motivated -- Is It All About The Money? Irene Abrams, Grace Leung and Ashley Stevens, Research Management Review, Vol 17 Winter/Spring 2010, in press

Finally, we are concerned about a recommendation in the recent report from President Obama's Council on Jobs and Competitiveness. The suggestion to allow research that is funded with federal dollars to be presented to any university technology transfer office, not just the one where the research has taken place (sometimes referred to as Free Agency) would actually slow the process of commercialization. The Free Agency concept would add a new layer of bureaucracy to the technology transfer process, including the need for agreements between the inventor's institution and the licensing agent which would add considerable time to the technology transfer process BEFORE marketing and licensing could even be started, as well as potentially reducing the inventor's share of royalties through management fees assessed by the licensing agent. The concept also assumes technology transfer offices would want to commercialize another institution's technologies, when in fact MIT, Stanford University and WARF (three of the largest and oldest technology transfer offices) have all publicly stated, "It would be inappropriate for us to handle inventions from inventors outside our own institutions, and we have no interest in doing so." The administration is right to recognize in the RFI that "It is a challenge to commercialize advances in the life sciences because of the risk…" The Free Agency approach to commercialization will create more risk in the eyes of companies which would normally invest in the technologies because untangling title and ownership would be more complicated and fraught with potential legal burdens

Clearly, the members of AUTM share the administration's interest in innovation. We share the priority of accelerating commercialization of university technologies, creating a stronger bioeconomy and are willing partners in seeking out new methods and improving upon standard practices. Thank you for the opportunity to respond to this Request for Information.

Sincerely,

Robin Rasor, CLP, RTTP
President

December 5, 2011

Office of Science and Technology Policy
BIOECONOMY@OSTP.GOV

RE: Response to Request for Information: Building A 21st Century Bioeconomy

In these challenging economic times, it is imperative that we continue to focus research-and-development investments in areas that will provide the foundation for future growth, and help the United States maintain its scientific acumen and leadership role in the biomedical enterprise. Given rising health care costs, targeted investment in mechanisms that promote the identification of appropriate treatments, and avoid unhelpful or detrimental ones that would nonetheless be expensive, are particularly timely.

It is for these reasons that I urge the Federal government **to invest in establishing the U.S.'s first national biobank of human biospecimens (tissue samples, tumor cells, DNA, blood, etc.) for use in cutting-edge research into new treatments for diseases.** The goal of such a bank would be to assemble sufficient quantities of high-quality, well-characterized human biospecimens to meet the demands of modern, technically sophisticated experimental designs and research platforms. Biospecimen quality can influence assay results profoundly, leading to incorrect diagnoses and inappropriate treatment decisions in the clinic or irreproducible results and misinterpretation of artifacts as biomarkers in the laboratory. Perhaps the most disastrous example of this is the finding that the amount of time a breast cancer specimen spends in formaldehyde fixative influences the readout of assays for estrogen and progesterone receptors in the tumor; patients with tumors positive for these receptors benefit from tamoxifen chemotherapy, whereas patients with tumors that do not express these receptors get no benefit from tamoxifen. Tumors that spend fewer than 6 hours or greater than 24 hours in formaldehyde erroneously appear negative for these receptors; this means that patients *who would have benefited* from tamoxifen treatment *did not receive it* because their tumors were unlucky enough to be improperly fixed. This problem went undetected for years due to inconsistencies in biospecimen handling and the lack of any standards for comparison.[1]

As medicine evolves and treatment decisions become more tailored to individuals' diseases, such examples will arise with increasing frequency unless a stable source of high-quality biospecimens is available for assay development and other research purposes. The gateway to choosing appropriate therapy in modern medicine is the diagnostic assay, and this raises the consequences for patients of poor biospecimen quality to an alarming degree.

[1] See Check W. 2006. Raising the bar for HER2 results. *College of American Pathology (CAP) Today* (December).

The idea of a national biobank was identified as one of ten ideas "changing the world right now" by Time Magazine in 2009, which highlighted the work of the National Cancer Institute's Office of Biorepositories and Biospecimen Research (OBBR). Unfortunately, cuts in government spending since then caused NCI to scale back its ambitions considerably. Rather than building a much-needed national biobank that would be a standard-bearer and engine for harmonizing the fragmented amalgam of biobanks in the United States, the OBBR has had to focus its more limited resources on supporting studies on how biospecimen variables influence assay results and the development of biospecimen standards. These efforts are clearly significant and much-needed, but they won't get us nearly as far as would access to a mother lode of high-quality, highly annotated human biospecimens to really jumpstart new discoveries.

Other countries (including Britain, Canada, Norway, Sweden, and Iceland) have already built national biobanks. Recently, the Chinese Ministry of Science and Technology committed to building a national biobank and supporting the development of the biomedical industry in China, with an eye toward the development of innovative drugs and treatments that will have a lasting, positive influence on cancer patients. Why is the United States sitting on the sidelines?

BACKGROUND

A major roadblock for translational research has been the difficulty in acquiring high quality human biospecimens—each linked to comprehensive epidemiological, clinical, biological, and molecular data—from a large number of donors. This difficulty stems in large part from the lack of standard approaches and wide variation in the collection, processing, and storage of biospecimens; the degree and type of data annotation; patient informed-consent procedures; access policies; materials transfer agreement conditions; and supporting informatics. A major obstacle has been "the lack of long-term secure funding for developing and sustaining biobanks and biobanking research."[2]

Recognizing that a national tissue resource, although ambitious, is necessary to realize the promise of genomics and proteomics for the prevention and cure of cancer and other diseases, the National Dialogue on Cancer Tissue Access Working Group, in collaboration with the National Cancer Institute, commissioned a National Biospecimen Network (NBN) Blueprint a **decade** ago with the following goal:

> *"to establish a national, pre-competitive, regulatory compliant and genetic-privacy protected, standardized, inclusive, highest quality network of biological sample(s) banks…that is shared, readily accessible, and searchable using state-of-the-art informatics systems (e.g., amenable to molecular profiling capability)."*

The Design Team of scientists, clinicians, industry representatives, and patient advocates outlined essential requirements and made specific recommendations for realizing the vision of the NBN Blueprint to be the first nationwide, standardized biospecimen resource designed to

[2] Vaught J, Rogers J, Carolin T, Compton C. 2011. Biobankonomics: Developing a sustainable business model approach for the formation of a human tissue biobank. *J Natl Cancer Inst Monogr*, 42: 24-31.

facilitate genomic and proteomic research. With the Blueprint in hand, the NCI took steps to realize this vision. The OBBR was established in 2005 and articulated a strategic vision for a national biobanking initiative, the Cancer Human Biobank (caHUB).

Human biospecimens can be considered the center of the personalized-medicine universe. They are the bridge between intracellular molecular information and clinical information. They enable researchers to study the molecular characteristics of actual human disease, and then correlate those characteristics with what is known about the clinical progression of the disease. Human biospecimens are thus integral to understanding disease mechanisms and identifying potential drug targets, developing diagnostic screening tests for biomarkers of a specific disease subtype, and identifying appropriate patients for testing new drugs and prescribing current ones. This vision is dependent on the availability of high-quality human biospecimens for screening, monitoring, and research. Without them, research and clinical assays are subject to the fate of the improperly fixed breast tumors described above: in other words, garbage in—garbage out.

POTENTIAL DEMAND AND VALUE PROPOSITION

Industry reports indicate that the global market value of the demand for human biospecimens and related services is growing between 20 and 30 percent annually, and was estimated to be approximately $200 million in 2009.[3] However, even though there are over 180 commercial biobanks in the United States, with samples from nearly 400,000 donors, no single company holds more than a 3 percent share of the global biobanking market.[4] The heterogeneity in collection approach and biospecimen quality discourages harmonization and seriously impedes the pace of the cutting-edge research we now have the technology to undertake. This is exactly the type of situation that presents an opportunity for government leadership: a public solution that facilitates access to appropriate quality and numbers of biospecimens for diverse research needs.

I write in my capacity as a public citizen, informed by my work as a contractor to the National Cancer Institute and past experience as an NIH program officer involved in multiple areas of science. Full disclosure: I was the managing editor and lead writer of the National Biospecimen Network Blueprint (September 2003), and beginning in 2004, Rose Li and Associates, Inc., has been providing science-writing services to the NCI and beginning in 2005 to the then-newly formed OBBR to support efforts to address the challenges raised by current biorepository practices and procedures. Rose Li and Associates, Inc., also provides ongoing programmatic support to many other agencies and offices at the National Institutes of Health, covering topics as varied as biology of aging, health and retirement, psychological disorders, neuroscience, genetics and pharmacogenomics, science of behavior change, health economics, and child health. Even in these diverse areas, it is surprising how often the topic arises of research being hampered by

[3] Vaught, et al. 2011, p. 25.
[4] The future of biobanks: regulation, ethics, investment of the humanization of drug discovery. *Business Insights*. March, 2009, as referenced by Vaught, et al. 2011.

inadequate access to high-quality human samples. I expect that all of these areas, and the U.S. economy, would benefit from the creation of a national U.S. biobank.

There is clearly a compelling need for a national U.S. biobank, a significant research infrastructure investment that would benefit a wide swath of research areas and clinical applications, as well as technology development. Its progress and usefulness could be objectively measured and the resulting discoveries tracked. According to Vaught, et al. (2011), "the value creation that a national biobanking resource would bring to the research community would, arguably, exceed the costs for developing and sustaining such an institution."

What is needed now is the political will and the investment of funds to realize the vision set forth a decade ago for the creation of a national U.S. biobank. This vision should be a distinct component of our National Bioeconomy Blueprint.

Sincerely,

Rose Maria Li, MBA, PhD
President and CEO

BROWN

CLYDE L. BRIANT
Vice President for Research

December 6, 2011

The Honorable John P. Holdren
Director
Office of Science and Technology Policy
Executive Office of the President
725 17th Street Room 5228
Washington, DC 20502

Dear Dr. Holdren:

Brown University appreciates the opportunity to comment on the Office of Science and Technology Policy's (OSTP) Request for Information (RFI) on the National Bioeconomy Blueprint. We believe this is a vital and timely national effort complemented by local efforts around the country.

We are witnessing the development of a successful bioeconomy right here in Providence, RI, spurred primarily by the research and the people emerging from our 12 institutions of higher education as well as through the involvement of the area's affiliated teaching and research hospitals. While there is already a significant amount of activity in the bioeconomy field, we are poised in Rhode Island to encourage greater progress in years to come if we make decisions wisely. The focus for this expansion is the Jewelry District in downtown Providence, formerly the world capital of jewelry manufacturing. This district which includes hospitals, Brown University's medical school and several of its research buildings, many emerging companies, and, importantly, developable land is in the process of being transformed into a Knowledge District with a locus of bioengineering, life sciences, health care, and green technology research. Where workers once made watchbands, scientists from Brown University and colleagues at other universities are now conducting research that will not only change lives but influence our understanding of the nature of life itself. They are investigating causes and processes of aging in human cells; examining the relationship of protein modification and abnormalities in cell structure to the development of disease; exploring links between cancer and chronic irritations caused by asbestos and other pollutants; and seeking affordable, universally accessible vaccines against AIDS, tuberculosis, West Nile Virus, and other infectious diseases.

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Biological research is the very foundation from which the bioeconomy must build its success, and any blueprint must incorporate an aggressive and robust research portfolio to bolster efforts to expand the bioeconomy. Earlier this fall, Brown University helped host a technology showcase to launch a Life Sciences hub for the state of Rhode Island. At the showcase, thirteen Rhode Island-based life science companies were selected to make brief presentations to a room packed with more than 250 attendees, more than 30 percent of who represented industry. Several other companies presented at the poster session. Over fifty licensable and/or collaborative projects were presented at poster sessions. The research that underlies these companies and promising technologies was performed at institutions across the state and with federal, state, and private funding. The event attracted entrepreneurs from Rhode Island and the region, venture capitalists, and scientists who were drawn together to learn about promising lifescience opportunities in RI and the emerging biomedical local and regional ecosystem.

Brown University is home to many of Rhode Island's leading biological sciences research initiatives. Two sites for the National Children's Study, an important and long term NIH-funded effort to improve the health and well-being of children, are led by Brown faculty in collaboration with Women and Infant's Hospital. Brown, in partnership with IBM, built a unique platform and public-private partnership, the Ocean State Consortium of Advanced Resources (OSCAR). OSCAR, with over fifty partner organizations, is a social infrastructure serving all sectors, disciplines and organizations and builds capacity to address RI's most challenging problems across health, energy, environment, and education. For example, OSCAR supports an effort, *Greening the Knowledge District,* that assesses the energy use and recommends strategies for sustainable development of the emerging Knowledge District where much of our growing bioeconomy activities are occurring and will continue to expand. OSCAR also supported regional partners in a successful application for a Broadband Technology Opportunity Program (BTOP) that will not only connect researchers regionally to accelerate their efforts but also this award will provide an estimated 200 jobs in the region.

The RFI on the National Bioeconomy Blueprint asked about six specific areas. Brown's comments in the areas relevant to the University's work are below.

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Grand Challenges

We believe there is not just one bioeconomy; it has many layers from international trade and commercialization, to regional efforts, to the local university. Addressing grand challenges requires an interdisciplinary approach, with input from individual researchers to large multidisciplinary centers. We recommend that grand challenges be identified through a fully interactive process involving Federal agencies, academia, and industry (similar to the process used to establish the National Academy of Engineering Grand Challenges for Engineering). Also, we recommend exploiting existing networks, such as the Rhode Island Life Sciences hub and OSCAR, to coordinate university, industry and non-profits to maximize the impact and address grand challenges. With its small size and existing collaborative networks, Rhode Island represents an ideal location for pilot projects within the bioeconomy blueprint.

Research and Development

Under this theme the RFI posed questions about priorities for high-impact research and innovation in a time of constrained Federal budgets. Brown University believes that traditional life sciences and basic research must be included in the bioeconomy blueprint. These provide the foundation for future innovation and train the future bioeconomy workforce. We recommend complementary approaches that include both single agency and multidisciplinary, multi-agency programs. For example, at Brown a National Institute for Environmental Health Sciences Superfund grant (initial award in 2005 and renewal in 2009) has supported a number of investigators from the traditional basic biology and engineering departments, and also has engaged researchers from the social sciences in support of its mission to address and resolve the scientific, engineering, and societal issues arising from the reuse of hazardous waste sites in Rhode Island. From this umbrella grant, our faculty have successfully competed for single-investigator funding opportunities from NSF, NIH, EPA, and state funding.

Also at Brown, our National Science Foundation-funded Institute for Computational and Experimental Mathematics is located in the same building as our Public Health Department and within proximity to the Rhode Island hospital system's core research facilities, as well as Brown's new Alpert Medical School building and a core molecular biology research facility in Knowledge District. This location leads to potential collaborations on issues such as gerontology research that brings together the extensive experience and expertise in clinical, basic science, and community-based research and Brown University and its teaching hospitals. Rhode Island, with its small scale and

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population and collaborative environment, is a great national platform for longitudinal studies to probe genetic and environment causes and determinants of health and disease. Additional multidisciplinary programs that support formal collaborations like this one would be high-impact and further accelerate ongoing federal efforts like the National Children's Study.

The Science of Massive Data initiative at Brown University is another program that supports the abovementioned multidisciplinary studies, as well as research on critical technical challenges that will accelerate bioeconomy-related research such as the specific question of how to deal with the overwhelming amount of DNA sequence information available to scientists. The explosion of data and data sources presents a grand research challenge in data-centric analyses, modeling, visualization, and information fusion. Tackling the data challenge will accelerate the learning curve, advance technologies and open new discipline-based pathways to explore data and translate it into innovative ideas and solutions. This Brown initiative develops partnerships between academia, government, and industry to advance innovative data-driven technologies and drive novel research and education models (including workforce development) to close the data to knowledge gaps.

Moving Life Sciences Breakthroughs from Lab to Market

<u>Barriers preventing translation of research discoveries to commercial markets</u>

The Bayh-Dole Act very effectively provides a legal framework for innovation at US universities to be captured, developed and turned into commercial products. By enabling academic institutions to control their intellectual property resulting from university funded programs and by providing universities with the legal authority to enter into exclusive licenses, the Act has been spectacularly successful at stimulating the development and commercialization of countless products. Especially at a time when economic forces are requiring large companies to scale back or even eliminate their internal research and development endeavors, products and technologies acquired by licensing are becoming increasingly important and even critical components for the commercial enterprise. Indeed, a significant proportion of drugs, medical devices and other commercial products developed over the last 20 years were based on developments and inventions made at research universities in the United States.

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Moreover, the number and magnitude of alliances between research universities and industry has increased over the last 20 years, thereby augmenting and leveraging the government's funding of basic research. These relationships are often based on patented inventions from university research.

Barriers that can prevent biological research discoveries from moving from the laboratory to commercial markets and that could represent areas to implement significant improvements include the following:

Education and training – University faculty often lack working knowledge about intellectual property and therefore do not recognize the potential commercial implication of their own work. The implementation of dedicated educational programs for students and faculty to teach and reinforce innovation and commercialization values would launch a mechanism to create a culture of innovation. Such programs would improve the wide capture of valuable intellectual property by stimulating disclosures and creative thinking on commercial development and focused, practical translational goals. At Brown, our masters program in Innovation Management and Entrepreneurship is one way we are educating students in this important area.

Collaborative agreements – Critical to a successful program for the translation of basic research discoveries from the academy into the public sector is the implementation of practices that reflect that discoveries from universities are very often early stage. Accordingly, agreements for commercialization often need to be flexible to ensure rapid and effective translation into the public sector. Risk-sharing and co-development types of structures should be considered that serve the function of being more palatable to industrial partners from the financial perspective, while mitigating the risk of licensing early stage innovations. If the technology results in a successful outcome the university and inventors can enjoy in the upside.

Bridging the development gap and lack of risk capital – Early stage technologies often encounter the so-called "development gap". In this case the mechanisms and initial insights might have been established in the academic laboratory using government funding, but additional proof of concept work is required before capital can be attracted for a start-up and/or a licensing partner to be brought on board. Funding for such translational work is sorely needed. Further, because early-stage investment in such programs is difficult to secure, government funded "venture" funds, perhaps with a longer-term horizon than traditional venture capital would be very advantageous.

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Suggested changes to SBIR and STTR programs for acceleration of commercialization of federally-funded research

The SBIR and STTR programs have been quite successful in providing critical funding for early stage companies to launch programs, expand their capabilities and develop products. Several concrete suggestions to improve the successful commercialization include the following: (a) allowing such grants to fund "pre-companies" – that is, to fund translational proof of concept work either at a university or contract research organization (CRO) in advance of a company being formed. (b) using a portion of funding under the SBIR/STTR program so that it is paired with outside (independent) business expertise. Thus, early stage companies would be treated to business review, assistance with focus on business/commercial goals and critical path, and ultimately have better access to capital.

Challenges associated with private-sector models for financing entrepreneurial bioeconomy firms

One of the principal challenges with currently available private-sector financing models is that the expected rates of return are sufficiently high that so-called "singles" and "doubles" (i.e. programs that might lead to innovative products, though not blockbusters) are not attracting investment. Although programs might be innovative and potentially satisfy market needs, they might not be big enough winners to be within the investors' rate of return spectrum. In addition, bio-science technologies take a long time to develop to fruition, so funding needs to have a long-term horizon. The Federal government should consider implementing programs to mitigate risk such as matching funding from the private sector (angels and/or venture capital funding).

Workforce Development

Brown University believes training for scientists and engineers should explicitly foster skills needed for the bioeconomy workforce. These skills include the ability to work in diverse teams that straddle expertise areas and disciplines, innovative thinking oriented around solving real-world problems, and communication with non-scientists. The National Science Foundation Integrative Graduate Education and Research Traineeship Program (IGERT) is an example of a Federal graduate training program that encourages mentorship, career development, hands-on experience with innovation, and translating research discoveries to solutions for societal challenges. These best practices should be

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expanded beyond the frontier interdisciplinary programs that IGERT supports to graduate training across the life and physical sciences and engineering.

Brown currently holds two IGERTs and a PIRE (Partnerships for International Research and Education) and so can attest first-hand to the value of these programs in developing the next-generation workforce of scientists and engineers. Two of these grants (the IGERT "Reverse Ecology: Computational Integration of Genomes, Organisms, and Environments," and the PIRE, "Millennium Village PIRE") are collaborations with the Marine Biology Laboratory (MBL) at Woods Hole, thereby providing our students opportunities to work with a diverse team of world-class scientists at both Brown and MBL. The second IGERT, "Development and Inequality in the Global South," draws on the University's strengths in social sciences to address key issues facing the world's growing population.

The Rhode Island EPSCoR is another positive workforce development program. It is led by a team of University of Rhode Island and Brown researchers and is focused on promoting collaboration and cooperation among the Rhode Island's institutions of higher education, including the Rhode Island School of Design (RISD). RI EPSCoR seeks to align its efforts with the needs of the state to increase research competitiveness, especially in marine life science and affiliated sciences. It does this with investments in infrastructure (specifically shared equipment) and education at the undergraduate and graduate student level.

Also, scientists and engineers in both academia and industry will need appropriate awareness of the interdisciplinary research questions central to the bioeconomy. It will be critical to train biological scientists with highly-developed quantitative skills as well as physical scientists and engineers with appropriate awareness of challenges in the life sciences. Also, programs that support network creation, workshops, travel, and summer programs for researchers are useful to raise awareness across scientific communities about science at the interface between disciplines. Fellowships that allow students to spend part of their graduate careers working in industry or other sectors help create networks between academia and industry, foster real-world learning, and provide students with greater understanding of workforce opportunities beyond the lab.

To promote commercialization of research breakthroughs, we recommend the government provide supplements to research grants if appropriate commercialization opportunities can be developed. For instance, the latest Department of Commerce i6 Green Challenge is a worthy initiative to spur the creation of proof-of-concept centers.

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We applaud funding for these types of centers but recommend that government and matching funds be available to support the development of commercial ventures, not just research teams from not-for-profit organizations. To help technologies get to the marketplace, proof of concept centers must be able to fund new commercial ventures once the innovation has "transferred" from the not-for-profit university laboratories.

To accelerate the commercialization of technologies within Rhode Island, Brown provided seed money to start the Rhode Island Center for Innovation and Entrepreneurship (RI-CIE), a collaborative state-wide effort to cultivate technology entrepreneurship. It helps Rhode Island-based entrepreneurs, researchers, and existing companies create, grow, and evolve new and sustainable technology ventures; promote commercialization of research and technology rising out of academic inquiry; and contribute to the state's economic benefit. RI-CIE has held over 200 educational and networking events in two years drawing over 5,000 attendees. RI-CIE supports an active network of close to 50 early-stage ventures. During the last two years, companies supported by RI-CIE have raised $8 million in public and private investment or grants. However, long-term support for RI-CIE is difficult to secure given the narrow focus of many federally commercialization programs.

Reducing Regulatory Barriers to the Bioeconomy

Brown University strongly encourages a streamlining of the regulatory requirements associated with Federal funding to universities through a revision of OMB Circular A-21. This action is timely and important, not just in reducing the burden faced by our researchers and staff, but also in recognizing the duplicative and wasteful nature of the current compliance environment.

We specifically call attention to the Council on Government Relations (COGR) and Association of American Universities (AAU) recommendations for elimination, or appropriate revision, of the current effort reporting requirements. At Brown, the burden associated with effort reporting spreads across a number of departments and divisions, involving both staff and faculty. In the central administration, 1.75 FTE's are dedicated to monitoring 31,000 effort reports annually costing approximately $145,000.

COGR and AAU have pointed out the duplicative nature of subrecipient monitoring. Entities funded by the Federal government, and subject to OMB Circular A-133 and to various compliance assurances (e.g., participation of human subjects, use of animals) are nonetheless required to also monitor each other when collaborating on research

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through subawards. At Brown, the labor intensive work of seeking audit reports, F&A agreements, and subrecipient profile questionnaires from over one hundred subawardees (who are already providing the identical information to their own auditors) is a tedious, labor intensive effort for no substantial benefit to the government or to the research partnership.

In order to assure the most effective and productive investment of Federal research dollars the duplicative and wasteful use of those resources, as well as those of university partners in the research enterprise, must be resolved. The substantial costs of effort reporting, and the redundant oversight required by subrecipient monitoring, should be eliminated. The government should conduct a careful review and reconsideration of excessive and repetitive financial reporting mechanisms such as ARRA, FFATA, and the proposed DATA Act (H.R. 2146), among others, as these mechanisms promise extraordinary additional data gathering and reporting burdens with very little real benefit for the government or the public.

Public-Private Partnerships

As mentioned above, the scale and collaborative environment of Rhode Island fosters successful public-private partnerships. Many of our most successful endeavors, like the Ocean State Consortium for Advanced Resources (OSCAR) and the Rhode Island Center for Innovation & Entrepreneurship (RI-CIE) described above, have at their core a public-private partnership. OSCAR and RI-CIE are excellent examples of regional collaborations of higher education, private industry, state and city leadership and members of the local communities. Both of these examples effectively draw leadership, funding, and human resources from the community to support their efforts and are making major contributions to the innovation ecosystems. Sustained, multi-year federal funding vehicles for the basic operations of these types of initiatives can significantly improve their effectiveness to act as catalysts for multi-institutional, public private partnerships.

These public-private partnerships also can be an effective means for the government to learn about barriers to commercializing technologies. OSCAR and RI-CIE have and will continue to play a major role in providing input and advancing discussions on policies and regulation related to intellectual property management, data transmission, patient safety, and privacy issues.

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Thank you again for the opportunity to comment on the RFI for the National Bioeconomy Blueprint. Brown University looks forward to a strong partnership with you in this endeavor and we are happy to provide further details or clarifications on any of our suggestions.

Sincerely,

Clyde Briant
Vice-President for Research

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To: The Office of Science and Technology Policy

The United States soybean industry, representing more than 600,000 U.S. soybean farmers, welcomes the opportunity to provide comments to be considered as you develop a blueprint for a new National Bioeconomy.

Since humans first settled in what is now the United States more than 15,000 years ago, the "economy" has been a *bioeconomy*. We harvested and traded wild-caught or farmed food and fiber, tools and fuel. What has changed over the past century is the efficiency of production systems necessary to fill the needs of a burgeoning global population while conserving limited natural resources.

With one outstanding exception – seafood -- our food is no longer wild-caught. Aquaculture provides a unique challenge and opportunity within the NEW U.S. *bioeconomy.* Below we outline the strategies for overcoming hurdles to an economically and environmentally sustainable aquaculture industry for domestic use and export that will both generate jobs and develop innovative technology.

1. *Commercialization and entrepreneurship opportunities to open new markets;*

The trade deficit attributable to seafood is $9 billion, which in terms of natural resources is second only to crude oil. More than anything else we eat, our seafood has traveled a long way - 84% is imported. Still, we eat half as much seafood as USDA recommends and research on the health benefits of long chain omega-3 fatty acids continues to emerge. While global production of fish from aquaculture grew more than 60 percent between 2000 and 2008, production in the U.S. remains stagnant.

As wild fish stocks continue to decline, there are myriad opportunities: for rural communities with long traditions of harvesting seafood (see for example developments in Maine); to repurpose or upgrade production systems for parts of the existing industry; to develop incentives for locally raised fresh fish production; and to expand demand for new products such as algae and co-products biofuel production that have the potential to be used as feed stocks.

2. *Research and development investments in areas that will provide the foundation for the bioeconomy*;

There are unique opportunities in aquaculture to apply advances in genomics and computational biology. Plant science research in the U.S. has been well-coordinated, but animal agriculture trails and the basic understanding of the interaction between plants and animals - nutrition - has scarcely begun. This is despite the fact that the economic and environmental sustainability of livestock production depends on efficient feeding.

Technological barriers (or conversely – opportunities) have been documented and vetted by DOC (NIST and NOAA). Innovation in production systems and fish nutrition presents many opportunities for exporting feedstocks, genetics and technology. But this improved understanding will also enable

producers in developing countries to use local crops to feed local species of fish – and seafood is a critically important source of protein in the developing world.

Research programs are already in place at NIH, NSF and USDA. Program managers just need to be given the impetus to develop "calls" for the interdisciplinary, innovative research needed to catalyze and focus innovation.

3. *Enhancements of workforce training to prepare the next generation of scientists and engineers for the bioeconomy jobs of the future*;

Historically, agricultural research in the United States has not been considered sexy science. But concerns about food shortages, land use, climate change and biodiversity have created a huge need for interdisciplinary researchers to use biotechnology to focus on agriculture. Delivering the dramatic increases in crop yields needed to feed 9 billion people by 2050 — without increasing greenhouse-gas emissions or encroaching on land needed to maintain biodiversity — is a daunting challenge that transcends disciplines and includes genomics, nanotechnology and soil microbiology.

But modern, technically sophisticated aquaculture also requires skilled workers to manage and operate facilities and trained scientists to staff research laboratories. There are opportunities to develop non-degree technical programs imparting the practical skills desired for employment at aquaculture production facilities.

4. *Regulatory reforms that will reduce unnecessary burdens and impediments while protecting health and safety, and the environment.*

The process of obtaining approvals and permits for coastal aquaculture projects is the major Impediment to the development of marine aquaculture in the United States. Permits from a spectrum of federal, state, and local agencies remains an uncertain, uncoordinated, unstable, and inconsistent process. There are constraints on siting that limit the expansion of shellfish aquaculture, particularly for small-scale producers. Legislation that would have streamlined the permitting process for federal waters has not advanced.

Technologies are available to monitor aquaculture operations as the basis for science-based regulations and to make the information available to the public on an ongoing basis. Environmental monitoring is expensive, however, and presents an opportunity for the public sector to partner with the private sector to provide the information the public demands.

5. *Public-private partnerships to accelerate innovation in key areas*.

Achieving the economic and environmental sustainability that would allow development and expansion of aquaculture in the U.S. depends primarily on continued commitments by government to provide a regulatory framework and strategic research investments. The U.S. soybean industry continues to use significant farmer dollars to work closely with NOAA and USDA to develop highly efficient alternatives to fishmeal and oil, the historical basis of formulated aquaculture feed. While we continue to work overseas to introduce aquaculture producers to soy-based aquaculture feeds and to expand the export of U.S. soybeans, we lament the significant opportunities to work within the U.S. to expand the supply of domestically produced seafood – and the jobs that will come with it.

There are many important opportunities to use biotechnology to optimize the efficiency and sustainability of U.S. soy production as global demand for soy for food and feed rises and soy becomes increasingly competitive with petroleum-based feedstocks. But, we consider expanding the U.S. aquaculture industry a uniquely exciting opportunity to focus the advances in biotechnology on a food production system that is growing globally, but not in the U.S. A vibrant domestic aquaculture industry

has the potential to provide health benefits as well as demand for co-products of biobased fuel production.

We welcome the opportunity to discuss these comments in more detail. Thank you for considering them.

Alan Kemper, President
American Soybean Association

Marc Curtis, Chair
United Soybean Board

Office of Science and Technology Policy

Request for Information: Building a 21st Century Bioeconomy

FROM: W. Steven Burke · President and CEO, Biofuels Center of North Carolina

SUBMITTED 6 DECEMBER 2011

TRANSMITTAL VIA EMAIL: BIOECONOMY@OSTP.GOV

The Administration has published a *Request for Information* soliciting input and recommendations for meeting national challenges in health, food, and energy while creating high-wage, high-skill jobs. Responses will be utilized in the development of a National Bioeconomy Blueprint.

I submit comments reflecting the experience and strategic recognitions of this Center in crafting a sustained, policy-based, comprehensive approach to biofuels development across our landscape.

BACKGROUND

The Biofuels Center strongly affirms the statement found in the solicitation that "(t)wenty-first century advances in biological research and technologies are poised to return tremendous benefits to the public." North Carolina's endeavor to develop a biofuels sector within our state is commensurate with the above recognition and will create widespread gain for our citizens.

By policy and strategy, North Carolina has committed to gain large capacity for biofuels and has set an ambitious goal: ***by 2017, 10% of the state's liquid transportation fuels will come from biofuels grown and produced internally.***

North Carolina's biofuels policy goal supports the national Renewable Fuel Standard mandate of 36 billion gallons of biofuels to be produced by 2022. This Center's approach addresses a recognition as simple in statement as challenging to implement: to meet that national goal, ***America needs new models to produce large amounts of liquid fuel from materials other than corn in places other than the Midwest.***

The nation at present lacks that model and those places. North Carolina is working within a logical approach to gain that model and verify that other states can create biofuels. In doing so,

this state works over time to create leadership, a new agricultural sector, new technology, large production capacity – and millions of gallons of fuel.

Committed state policy and the comprehensive approach described below are judged a strong and necessary foundation. Technology and production companies have taken note as they seek new sites nationwide.

DEVELOPMENT OF THE BIOFUELS SECTOR: A GRAND CHALLENGE

The *Request for Information* calls for the identification of "grand challenges"— areas and issues that will transform the Bioeconomy in health, energy, the environment, and agriculture. North Carolina, presuming to trigger statewide the transformation from a fossil fuel based transportation sector to a biofuels based transportation sector, is well aware of both the importance and the enormity of such societal challenges.

Creating a new biofuels sector across North Carolina is an enormous long-term task for three reasons:

- In 2007, upon establishment of the Biofuels Center, North Carolina had minimal biofuels capability and gained no attention from technology and production companies.
- Creation of an agriculturally-based, complex, expensive and enormous new sector and new technology across the landscape is unprecedented and without model.
- Because corn is by policy not the foundation for biofuels in North Carolina, other feedstocks available sustainably, in quantity, and with economic return must be gained.

Development of a new biofuels endeavor across North Carolina is without precedent in complexity of tasks and implications, but possible if a key recognition underlies policies and activities: development of large biofuels capacity must be seen as **landscape changing**, actually and figuratively, and as such must be judged nothing less than **a societal and civic imperative**. Gaining that capacity, after all, necessarily synthesizes key components of civic society: energy, agriculture, policy, environment, technology, economic gain, and provident preparation for the future.

Such thinking, both bold and common-sensical, shapes work of the Biofuels Center. The Center's endeavor and approach spring from four compelling and strong imperatives:

- Smart places and leaders now must strategically address their energy future as crucial for their future success and daily survival.
- An enormous and feasible new sector, well matched to a state strong in both agriculture and technology, will be created.

- Economic and societal gains will come across the state, largely in rural and agricultural counties most in need of economic advantage. Realistic opportunities for sustained rural gain are few and merit continued support.
- Job and economic enrichment will be as strong or stronger in existing areas – forestry, agriculture, logistics and distribution – as in new production facilities.

A Comprehensive Approach

Judged the nation's only agency working comprehensively over time for all aspects of biofuels development, the Biofuels Center was established to meet the state goal and shape a 10-15 year civic endeavor statewide.

North Carolina's approach to biofuels development is comprehensive, based on the recognition that piecemeal attention to resources and tasks yields uncertain success. A dovetailed framework of strategy and activities must integrate every aspect of biofuels development, from governmental policy to land and consumer choice.

The nation's only state-based agency constituted with a comprehensive mandate, the Center addresses over time: research, growing and agronomic analysis, pilot and large scale production, company development, distribution, land use, environmental and policy issues, and public education.

Specific requirements are varied, including: farmers and landowners must commit to new feedstocks and new uses of biomass; economic analyses must verify that money can be made in growing, production, and distribution; consequential issues must be addressed, for large impact will be seen on land, biodiversity, water, and the environment; policy commitment must be sustained through years, political changes, and the setbacks inevitably handmaiden to new technology.

Federal and State Policy

Sustained and committed federal biofuels policy has never been more important. That policy imperative is now threatened by budgetary problems and short-sighted vantage points. Articulation and defense of national goals to maintain the Renewable Fuel Standard – the sensible imperative and foundation for biofuels goals nationwide – is imperative. Consistent and strong biofuels programs and funding from the Department of Energy (DOE) and the Department of Agriculture (USDA) are now more critical than ever. A nation confronting the

profoundly significant cusp from a fossil fuel based sector to a biofuels sector requires cohesive commitment, sustained support, and policy certainty.

Federal programs managed by DOE and USDA strengthen the biofuels sector and verify the value of purposeful biofuels development for rural economic gain, greenhouse gas reduction, and energy independence. In particular the USDA loan guarantee programs for biorefineries are critical to the development of the biofuels industry in North Carolina as nationwide. Other innovative programs, such as the Biomass Crop Assistance Program, also provide needed support to this nascent industry.

At the same time, biofuels – because potentially to be gained from so many places with equal and not necessarily competitive success – can impel increasingly deliberate attention within the life and goals of states, yielding both need and gain. State biofuels commitment can augment and support federal programs. Doing so enables a return to a clearly necessary model of more local fuel production. States can shape policies and support, as we are working to do in North Carolina.

The *Request for Information* correctly recognizes public-private partnerships as requisite to build the bioeconomy. The Biofuels Center implements that approach through widely varied multi-party projects, on the reasonable premise that both societally significant changes and new technologies are never gained from a single vantage point or entity. Among the most nationally resonant of such projects is development North Carolina's Biofuels Campus, located on 426 acres of farm and forest land within 30 miles of the nationally renowned Research Triangle Park.

SHARED IMPERATIVE

A bioeconomy shaped by both vision and practical strategies can indeed vitalize America's workforce and economy. In North Carolina, long-term and purposeful commitment to both biofuels and biotechnology well verifies that expectation.

Having learned much about development of a statewide biofuels endeavor, this Center will with pleasure share experience and ideas with the Administration in implementation of the Bioeconomy Blueprint.

W. Steven Burke

President and CEO · Biofuels Center of North Carolina

[redacted]

To:
Dr. John P. Holdren
Director, Office of Science and Technology Policy
Executive Office of the President
725 17th Street NW, Room 5228
Washington, DC 20502

Submitted Through: bioeconomy@ostp.gov

From: Claude R. Canizares
Vice President for Research and Associate Provost, Massachusetts Institute of Technology (MIT)

Date: Dec 6, 2011

Subject: Recommendations Concerning Bioeconomy Blueprint; Request for Information

Dear Dr. Holdren:

I am writing in response to the Office of Science and Technology Policy's (OSTP) October 7, 2011 Request for Information (RFI) regarding the development of a National Bioeconomy Blueprint.

We very much welcome the opportunity to comment on the bioeconomy framework. We believe key to this idea is convergence, or the merging of the life and physical sciences with engineering, as a superstructure to support the next stage of advance in a host of areas. This response will focus on the portion of the bioeconomy blueprint related to the future of biomedical research and the opportunities lingering at the intersection of existing efforts.

Background

Leading MIT researchers recently published a white paper entitled, "The Third Revolution: The Convergence of the Life Sciences, Physical Sciences, and Engineering (2011)," which outlines the way forward for biomedical research.[1] This white paper builds on the National Academies report, "A New Biology for the 21st Century: Ensuring the United States Leads the Coming Biology Revolution (2009)."[2] This effort is also strengthened by additional reports including a recent Food and Drug Administration (FDA) report, "Driving Biomedical Innovation: Initiatives for Improving Products for Patients (2011)"[3] and the recently released National Academies

[1] The MIT paper is available online at http://web.mit.edu/dc/Policy/MIT%20White%20Paper%20on%20Convergence.pdf
[2] The past NAS report is available online at http://dels.nas.edu/Report/Biology-21st/12764
[3] The FDA report is available online at: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274333.htm

report, "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease (2011)."[4]

As MIT Professors Phillip Sharp and Robert Langer explain in the July 2011 *Science* article[5] outlining the convergence framework:

> The next challenge for biomedical research will be to solve problems of highly complex and integrated biological systems within the human body. Predictive models of these systems in either normal or disease states are beyond the capability of current knowledge and technology…there is an increasing need to merge expertise that goes beyond the interdisciplinary intersection of fields to the emergence of new disciplines. In recent decades there have been two biomedical revolutions: molecular biology and genomics. We believe the convergence of fields represents a third revolution (1, 2), where multidisciplinary thinking and analysis will permit the emergence of new scientific principles and where engineers and physical scientists are equal partners with biologists and clinicians in addressing many of the new medical challenges….[C]onvergence will be key to advances in many crucial areas, such as using microfabrication to analyze single cells, the development of targeted nanoparticle therapeutics, the integration of large data sets to create personalized medicine at the bedside and microsensors that can detect the onset of disease.

We envision convergence as an organizing framework for understanding pathways to move forward through a bioeconomy blueprint.

Section 1: Grand Challenges

As you know, the current state of medicine is such that costs are high and biomedical investment is not perceived to be lowering those costs. On top of that, we are facing the demise of blockbuster drugs. Despite the genomics revolution, medicine is still intrusive and not specifically targeted. Given the reality that the U.S. spends a larger portion of its gross domestic product (GDP) on health care than any other industrialized country; that a quarter of the Medicare budget is spent in the last year of life; and that, relative to GDP, the total U.S. investment in research and development (R&D) is falling in comparison to emerging global leaders, we have to change the paradigm for biomedical research to help reverse these trends.

In accordance with changing the paradigm for biomedical research and in keeping with the grand challenges identified by President Obama, (including smart anti-cancer therapeutics, early detection of disease from saliva samples, and advanced regenerative medicine for organ transplants), we propose one grand challenge with several short term challenges within.

The grand challenge we suggest tackling is to replace symptomatic disease with prediction of disease.

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[4] The recent NAS report is available online at: http://dels.nas.edu/Report/Toward-Precision-Medicine-Building-Knowledge/13284

[5] Phillip A. Sharp and Robert Langer, "Promoting Convergence in Biomedical Science," Science 29 July 2011: Vol. 333 no. 6042 p. 527. This article is available online at http://www.sciencemag.org/content/333/6042/527.short

Prediction of disease would allow treatment before disease symptoms manifest to the patient. Based on this model, individuals would be scanned for diseases continually and treated at the first cellular indication, before the onset of manifested symptoms. This idea takes the concept of prevention to a new and more active stage.

This would require an integration of data into models of disease states that have predictive value at the level of an individual. In order to address this challenge, we need to advance the science of normal and disease states, integrating medical records, genomic data, understanding of the systematic structure of cellular processes, and environmental and clinical data from individuals to create models to predict disease states as well as their prevention or treatment.

In addition to related technology advance, three areas in which to begin this work are briefly outlined below.[6]

- **The Single Cellome.** We should focus on what we don't know. Start with enhancing current understanding of health and disease by complete understanding of the healthy and diseased cell and its components as well as how it reacts to its environment.

- **The Human Phenome Project.** We need to get ahead of disease. Change the medical paradigm to less physically intrusive, continuity-inspired medicine. This will include high throughput parallel analysis at multiple stages including imaging methods that detect metabolism at the level of individual cells.

- **Living Laboratories**. The current animal models are insufficient to enable to next stage of advance. We need to develop effective methods of analyzing human systems. This includes the development of sophisticated human tissue, even whole organ systems, to characterize normal and disease processes.

While academics and practitioners work towards these advances, there are concrete steps government can take to help achieve this goal. Several recommendations are outlined below.[7]

<u>Recommendations: The Federal Role</u>

- **Establish a biomedical innovation culture within government based on the convergence framework.** Scientific research has historically been funded in separate stovepipes by science-mission agencies. Mechanisms to enable and foster better connections need to be institutionalized. One option is to establish think-tank environments within each research agency where agency detailees from across the executive branch could be invited to visit and collaborate on the research priorities of the host institution. This might be initially be coordinated by the National Science and Technology Council (NSTC).

[6] These concepts were outlined during a daylong convergence workshop at MIT on September 30, 2011 that included representatives from academia and industry, as well as agency leaders and Boston-area clinicians.
[7] These recommendations have been adapted from a selection of recommendations included in the MIT White Paper, "The Third Revolution: The Convergence of the Life Sciences, Physical Sciences, and Engineering." That paper is available online at http://web.mit.edu/dc/Policy/MIT%20White%20Paper%20on%20Convergence.pdf

- **Support a diverse portfolio of federal government investment.** Individual investigator grants for smaller projects are a time-honored, respected tradition. Small projects often lead to innovation and new discoveries, and support for them should continue. At the same time, it is vital to also direct resources to large-scale projects that include multiple principal investigators. These undertakings allow researchers from many disciplines to conduct systematic inquiries into general target areas while pursuing their own specific interests.

  Since collaboration and innovation in research methods are more difficult if individual researchers are isolated in separate departments at their institutions, we suggest the founding of centers at institutions across the country that would include multiple principal investigators. A group of agency and academic experts should convene and use a systems approach to design these centers around national research priorities.

- **Educate, expand, and support the next generation of researchers based on the convergence model.** Universities increasingly understand that the merger of scientific and engineering fields is a reality for the successful future of the life science enterprise. New efforts need to be undertaken to educate the next generation of researchers to work in cross-disciplinary fields. While a deep disciplinary background remains vital, including a robust cross-disciplinary education is essential additional preparation for our future scientists. A promising example of a program that currently enables such collaborative learning, and that can encompass convergence approaches, is the National Institutes of Health (NIH) Training Grant. We recommend that the training grant model be expanded and also utilized at other agencies.

  In addition, we must strengthen the pipeline of future researchers by addressing the diversity problem in our educational system. To that end, careful consideration should be given to the recommendations contained in two recent studies, including the 2009 report by the Council on Graduate Schools (CGS), "Broadening Participation in Graduate Education,"[8] and the 2010 report, "Gender Differences at Critical Transitions in the Careers of Science, Engineering, and Mathematics Faculty"[9] released by the National Academies.

Section II: Research and Development

The ambitious goal, as described in the previous section, of bringing an end to symptomatic disease would require the scientific community to unite across existing siloes and examine the promise lingering at the intersections of current efforts. Such a battle cry could offer momentum to a coordinated cross-agency effort that would move national competencies and capabilities closer to realizing the promises made for the genomics era and the era of personalized medicine.

We would recommend that the Office of Science and Technology Policy (OSTP) convene a cross-agency working group through the National Science and Technology Council (NSTC)

[8] More information about the CGS report is available online at http://www.cgsnet.org/default.aspx?tabid=365
[9] The NAS report is available online at http://www.nap.edu/catalog.php?record_id=12062

mechanism to take steps towards such a goal.

Section III: Moving Life Sciences Breakthroughs From Lab to Market

One of the aspects of technology commercialization that the Office of Science and Technology Policy (OSTP) should consider in its bioeconomy effort involves enhancing and overcoming impediments to university technology transfer. In response to the National Economic Council and Office of Science and Technology Policy's March 25, 2010 Request for Information (RFI) on Commercialization of University Research, Dr. Susan Hockfield, MIT President, offered a detailed explanation of the MIT innovation ecosystem with specific recommendations for broad application of this successful model.[10] The recommendations discussed below draw on those proposals.

Recommendations: Fostering Commercialization through the University Innovation Ecosystem

The following recommendations for government action would enhance the impact of federally funded research and improve the process of transferring research in the lab to commercialization by the private economy.

- **Implement Model Innovation Centers.** Implement additional pilot model innovation centers across the U.S. at research universities to develop, document, and assist in nationwide dissemination of "best practices" for encouraging innovation and entrepreneurship by students, faculty, staff and alumni. This could include expansion of the new National Science Foundation (NSF) I-Corps effort, but additional models as well. The pilot centers, for example, could more closely draw on MIT's Deshpande Center approach of close proximity between researchers and advisors. They would engage in a variety of activities including connecting university researchers with technologies of potential commercial value to industry and capital; educating and mentoring; business plan preparation; creating ties to regional businesses; and providing grants or seed money. These centers would also disseminate best practices and form the nucleus of a community amongst U.S. universities enhancing innovation.

- **Support On-Campus Mentoring Services.** Support expansion and escalation of mentoring services based on the proven MIT Venture Mentoring Service model at research universities across the U.S. Additionally, support formation of an Innovation Mentoring Consortium that would enable the sharing of knowledge, experiences, and best practices amongst mentoring organizations to enhance effectiveness and further increase innovation output.

- **Add Technology Transfer Costs to Indirect Cost Pool**. Many schools, particularly in the current economic climate, lack funding to build a patent portfolio and employ well-trained staff to create successful technology transfer offices. Many existing offices are now facing cutbacks. Allowing technology transfer costs (e.g., patents and staff) to be included in the indirect cost pool for federally funded research (and perhaps excluded

[10] Please refer to the full comments, "Recommendations Concerning Commercialization of University Research; Request for Information - May 26, 2010," online at http://web.mit.edu/dc/policy.html

from the administrative cost cap) could provide schools with the resources to bolster and build their Technology Licensing Office (TLO) programs.

At the same time, federal programs (including at the National Institutes of Health, Departments of Energy and Agriculture) are increasingly asking for "matching funds" or cost sharing from non-profit universities for infrastructure and applied research. This is a very detrimental move in the wrong direction, and these cost-sharing policies should be reversed. University funding streams, unlike those in the private sector, do not have a profit pool that could be allocated to such sharing.

- **Promote Policies that Encourage Entrepreneurship**. Encourage government and universities to examine their rules and regulations to eliminate barriers to responsible faculty/staff entrepreneurship. Medical schools and teaching hospitals have high potential for entrepreneurship that could benefit society broadly, while also contributing to economic growth, consistent with high standards of integrity. In those institutions, policies that strongly promote openness of relationships, appropriately overseen by senior faculty committees, can ameliorate the potential problems that arise from the needed medical faculty connections to biomedical industry.

- **Host Technology Innovation Fairs**. Federal R&D agencies involved in bio-medical research should cooperatively consider holding joint annual technology innovation fairs that bring groups of outstanding university inventors together with supporting government agencies, companies, venture capital (VC) firms, and financial institutions in emerging technology sectors. The recent Advanced Research Projects Agency – Energy (ARPA-E) Energy Innovation Summit could provide a very useful model.[11]

- **Support Small Firm/University Collaborations**. Encourage research agencies, where appropriate, to adopt the Defense Advanced Research Projects Agency (DARPA)-hybrid model for a portion of their funding as part of their research and development (R&D) portfolios. This approach provides awards for collaborative efforts involving small firms and university researchers. This would be especially useful at the National Institutes of Health (NIH); the proposed National Center for Advancing Translational Sciences (NCATS) could pilot this approach there.

- **Examine How to Attract More Venture Capital Investment.** While this Request for Information (RFI) is seeking solutions that fill in the gaps of venture funding and finance, and alternatives to them, there is much more we need to understand about capital availability in this sector. Accordingly, there is a need to conduct an in depth data-based examination of the factors that induce Venture Capital firms (VCs) to invest in early-stage technologies, and the structure and stability of that funding. Typically, for example, VCs only invest in physical-science-based technologies when they are near commercialization, yet life science advances will increasingly need to rely on engineering physical science developments and longer term funding may be required for these. They invest in relatively fewer startups during economic downturns creating significant

[11] Further information on the ARPA- E Energy Innovation Summit is online at http://www.ct-si.org/events/EnergyInnovation/

instability; we need to consider what factors are leading to these decreases in VC investment rates. If these issues are studied and better understood incentive systems could be devised to influence these trends.

- **Encourage SBA Investment in New Technology Startups.** Examine the policies of the Small Business Administration (SBA) to be sure that adequate emphasis is placed upon new businesses with high growth potential (i.e., "gazelles"). In particular, there should be an explicit focus in agencies' administration of the Small Business Innovation Research (SBIR) Program for new technology startups and new business recipients that will accelerate technology implementation.

- **Enhance and Add Tax Credit Programs to Encourage Technology Transfer.** In addition to improving some of the structural problems in the research and development (R&D) tax credit and making it permanent, provide additional credit for funding for collaborations between industry and university researchers to accelerate technology transfer. This is available now for energy technologies and should be extended more broadly, including to bio-medical research firms. Also consider dropping the incremental feature of the current credit, so it rewards significant, sustained R&D investments by firms. We refer you to work completed by the Information Technology & Innovation Foundation (ITIF) on this subject, including a recent overall report, "Expanding the Research and Development Tax Credit to Drive Innovation, Competitiveness and Prosperity."[12]

- **Provide Post-Degree Visas**. Foreign-born immigrants have an unusually strong record of starting firms and bolstering our science talent base. This has long been an historic competitive advantage for the U.S. that few nations have been able to match. We rely heavily on foreign-born post docs in the health science area, in particular, and also offer graduate education to many from abroad. These are important talent pools we should encourage to stay in the U.S. In order to preserve this strength, the U.S. should award five-year, post-degree visas to all foreign students in accredited university programs in STEM and management fields. These special visas should be converted easily into green cards, and their holders fast-tracked to U.S. citizenship if they continue employment in U.S. science and technology-based research and enterprises, or if they start their own U.S.-based companies.

Section IV: Workforce Development

We applaud the President's efforts on workforce development with community colleges earlier this year with his announcement of the expansion of the Skills for American's Future Initiative. We agree that industry partnerships with community colleges across the country can build a nation-wide network that could maximize workforce development strategies, job training programs, and job placements. As part of that effort, we also applaud the launch by the Manufacturing Institute, the affiliated non-profit of the National Association of Manufacture

[12] The ITIF report is available online at http://www.itif.org/publications/expanding-research-and-development-tax-credit-drive-innovation-competitiveness-and-pros

(NAM) of a certification program between industry and community colleges.[13] In the biomedical field, production remains a significant portion of pharmaceutical and device costs; community college certification developed in coordination with biopharma firms for skills needed in this sector could be an important effort.

Section V: Reducing Regulatory Barriers to the Bioeconomy

MIT views the regulatory science effort underway at the Food and Drug Administration (FDA) as critical to improving regulatory delays and barriers for drug and device approvals.

Concerning university research, there are two specific areas of regulatory burden that continue to affect efforts to participate in what is described as the bioeconomy. These include agency and university shared research expenses via the ongoing A-21 discussion, as well as conflict of interest regulations as most recently exemplified by the National Institutes of Health (NIH) regulations on this issue.

Regarding specific recommendations, we refer you to the comments on A-21 submitted in July 2011 by the Association of American Universities (AAU) to the A-21 Task Force of the National Science and Technology Council (NSTC).[14] Regarding the conflicts of interest issues, we refer you to the ongoing work of the Council on Governmental Relations (COGR), and specifically to the document COGR prepared in response to the NIH proposed regulations in 2010.[15]

Section VI: Public-Private Partnerships

The highest impact opportunities for public-private partnerships related to the bioeconomy revolve around data. Applying the convergence framework to shared pools of existing data would revolutionize the capacity and scope of biomedical research. For instance, it would enable progress in validating surrogate markers, advancing predictive toxicology, and identifying and validating predictive clinical biomarkers (genetic and other) of response. Enriched data sets would also advance efforts to map established outcomes to observational, clinical, and lab data, and to learn about disease sub-types from data.

Regarding specific improvements in the regulatory process for drugs, diagnostics, and devices, the NEW Drug Development ParaDIGmS (NEWDIGS) program at MIT is working towards leveraging drug data to deepen collective understanding of progressive or adaptive licensing approaches through retrospective simulations. Given further access to the pool of data held by federal agencies, MIT researchers would seek to simulate adaptive licensing designs on historical cases of drug development to understand impact on time, risk of late stage attrition due to safety issues, economics and public health impact. This effort would be unique since the simulation would include all key stakeholders to understand perspectives of regulators, pharmaceutical companies, payers, providers, patients, and public health personnel.

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[13] More information available online at http://www.whitehouse.gov/the-press-office/2011/06/08/president-obama-and-skills-americas-future-partners-announce-initiatives

[14] The AAU A-21 Task Force letter is available online at http://www.aau.edu/WorkArea/DownloadAsset.aspx?id=12432

[15] The COGR response to the NIH Conflict of Interest Regulations is available online at http://www.nacua.org/documents/COGR_Comments_NIH_COI_ProposedRule.pdf

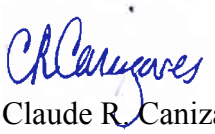
In addition, since manufacturing and clinical outcomes are currently completely siloed, the MIT Biomanufacturing (BioMAN) Program at the MIT Center for Biomedical Innovation (CBI) would be interested in understanding the relationship between outcomes data in clinical trials (safety, efficacy, immunogenicity) to manufacturing process information.

These shared pools of data would drive advancements in ongoing research and would also enable important new questions to be explored. However, a public-private process with access to university expertise is the only way this data will get unlocked and become truly accessible for research. The federal government could play a key role both as a convener of public/private interests and as a leader in unlocking access to data across federal agencies.

In closing, I want to express MIT's appreciation for the recognition and efforts of the Office of Science and Technology Policy (OSTP) to help frame research as an economic driver. As explained in the introduction, we believe the bioeconomy blueprint efforts correspond closely with efforts underway at the National Academies (NAS), National Institutes of Health (NIH), and the Food and Drug Administration (FDA) and among a growing number of universities across the country manifesting their own version of the convergence model. This culmination of these efforts indicates that we are at an inflection point for life science research that, if navigated correctly, could encompass new fields of knowledge and yield revolutionary advances in a wide array of areas.

I hope you find this submission useful in developing the National Bioeconomy Blueprint. MIT's faculty and staff stand ready to assist you as you move forward in these efforts. If your offices have any follow up questions, please contact Amanda J. Arnold in MIT's Washington, DC Office at [redacted]

Sincerely yours,



Claude R. Canizares

Response of Bruce W. Stillman to Office of Science and Technology Policy Request for Information re: Building a 21st-Century Bioeconomy

I welcome the Administration's announcement of its intention to draft a National Bioeconomy Blueprint, and wish to submit several "grand challenge" suggestions, as requested by OSTP.

1. Launch a national Cancer Therapeutics Initiative

There is an outstanding opportunity to apply recent scientific and technological advances to the development of new classes of anti-cancer drugs and diagnostics, and do so much more rapidly and cost-effectively than has been possible heretofore. Such an Initiative would leverage information gleaned from the National Cancer Institute's Cancer Genome Atlas project, and would move beyond it in important ways to rapidly transform recent basic science discoveries into targeted therapies that address the disease's genetic and epigenetic diversity.

Comprehensive knowledge of mutated cancer genes in major tumor types will not in itself enable us to halt cancer. Using revolutionary RNA interference-based screens, we now, however, have the ability to identify the Achilles' heels of tumors in an unbiased fashion; this enables us to discover factors of all kinds, and not just those with gene mutations, that drive cancers in patients. These factors, including a plethora of cellular proteins with no previously known connection to oncogenesis, constitute an entirely new pool of potential drug targets. Especially exciting is the fact that we now possess the tools, notably animal models, with which to validate these targets in a preclinical setting that closely reflects the human clinical experience. A second phase of the Initiative would focus on discovering drugs against the new targets and testing them in the same model systems. Because these models are based on human cancers, this should significantly increase the probability of clinical success. Furthermore, by identifying patient-specific targets and drugs during pre-clinical testing, this system is likely to reduce costs by requiring far fewer patients to be enrolled in trials. This Initiative has the prospect of generating targeted, non-toxic therapies against a broad range of cancer types and subtypes over the next decade, including those we have had little success in treating such as cancers of the blood, brain, lung, prostate, ovaries, pancreas and liver.

2. Make a major commitment to fundamental neuroscience

As vividly documented by the National Institute of Mental Health, the costs of mental illness in the United States are extraordinary. Quite apart from the impact upon national productivity there is the incalculable human cost to victims and those who love and care for them, often over periods spanning decades. We need to make a major investment in basic research in neuroscience and related fields because, to be frank, they are *one to two decades behind* the state-of-the-art in fields now at the forefront of biological discovery, most notably cancer research. We are in a position to achieve the objectives of the cancer initiative sketched out above precisely because our basic understanding of cancer and related cell biology and genetics has advanced so far, especially since the completion of the Human Genome Project. Our near-term (5-to-10-year) aim in a basic science initiative in neuroscience should be to attain a much more detailed understanding than we

presently have of the biological correlates of cognitive dysfunction, and in particular, knowledge of the neural networks and cellular and intracellular pathways causally involved in major disability-causing mental illnesses including autism, schizophrenia, depression, and the family of stress- and anxiety-related disorders including post-traumatic stress disorder. The near-term fruits of acquiring such understanding likely will be our first reliable and objective non-invasive diagnostics for common mental illnesses and much better quantitative measures of these illnesses, which will help pave the way toward new treatments.

3. Invest in basic plant science, to address energy and food needs

Our fundamental knowledge of plant life, like that of the workings of the brain, is lagging. Our federal government should commit to the grand challenge of significantly increasing funding for basic plant science, with the specific aim of generating the knowledge we need to produce commercially viable biofuels and to increase yields of food crops. We have made some progress on biofuels in recent years, but still lack fundamental knowledge that has the potential to transform the efficiency, and therefore economics, of biofuel production. Basic research is needed to increase the photosynthetic efficiency of plants and algae to optimize the use of available sunlight in converting light into carbon. Complementary basic research is needed to determine how to convert the fixed carbon into lipid and oil and store that oil in vesicles before harvesting for biofuel. At the same time, with the global population recently having passed the 7 billion mark – on its way perhaps to 9 or 10 billion – we should be neither naïve nor complacent about future food needs. The United States should be at the forefront of applied research in plant science, but can only achieve this if we significantly increase funding right now in basic plant science.

4. Continue to invest in the training of scientists

Our federal government must not fail to invest in training the next generation of scientists if The United States is to remain at the cutting edge. All of the initiatives and investments outlined above are predicated upon the assumption that we will continue to be a magnet for the finest young people who choose to devote their talents to advancing scientific knowledge. With cutbacks looming in NIH funding, training programs are often the first things eliminated. We must make certain that this does not happen, or risk losing our preeminent status in the sciences.

5. "Applied science" goals must not be pursued at the expense of basic research

The initiatives and efforts outlined above each depend upon continued robust funding of basic science. Grand challenges can help clarify our priorities, and applications of new knowledge must be vigorously pursued. But *we must not do so at the expense of basic research*. All that we accomplish in applied science, from developing more effective cancer treatments to inventing new biofuels and crops that will adjust to climate change, is possible because of advances we have made in fundamental biological understanding. Such advances, like the discovery of RNA interference, cannot be predicted. But we can say with confidence that they cannot and do not occur absent robust investments in basic science and in the training of new scientists and members of the technology workforce. A vivid example of how such investments pay off is the Human Genome Project, which not

only gave rise to the novel field of genomics, but also, as the Battelle Memorial Institute has estimated, generated $796 billion in direct and indirect economic activity within the first decade since its completion. This includes some $244 billion in personal income and an impressive 3.8 million job-years of employment.[1] Considering the federal government's investment of $3.8 billion in the HGP through 2003 (less than $6 billion in current dollars, and an amount now recouped *annually* in genomics-related taxation alone) the return on investment has been $141 for every $1 invested. This investment in basic science – made without a guaranteed practical benefit – has not only been the single most influential investment made in modern science, but must rank as one of the wisest ever made in any American undertaking.

6. A cautionary word: Against institutionalization

In funding major scientific initiatives we must take pains not to establish infrastructures that become permanent. It would be a mistake, in our view, to institutionalize grand challenges. Each that is undertaken should be pre-planned to have a ramp-up and ramp-down phase. It is also vital that each initiative be peer-reviewed, to insure both the integrity and appropriateness of the investments that are made.

Sincerely,

Bruce W. Stillman, Ph.D.
President
Cold Spring Harbor Laboratory

[1] Battelle Memorial Institute, "Economic Impact of the Human Genome Project," May 2011, p. ES-2.

A Blueprint for A National Bioeconomy

Alan S. Rudolph

There is now common acceptance that the 21st century will be dominated by discoveries and application of life sciences. This aggregate movement is led by the integration of biological sciences with many disciplines from mathematics and physics to materials and chemistry. As these traditional boundaries have come down, the ability to drive new innovation into real technological solutions that offer significant economic US competitive advantage have emerged. Nurtured by over 2 decades of investment in interdisciplinary life sciences research, biotechnology investments in the venture community, new intellectual discovery and emerging markets have been created in health and medicine, education, human performance, energy conversion, and in bioengineering design of new materials. While it took nearly a decade to begin to realize the centuries first disruptive discover, the human genome, the expanse of information technologies and accessibility has increased the rate of movement of interdisciplinary life sciences into realizable contributions to economic gains. This treatise examines select key areas that could provide significant stimulus and grand challenges to enhanced opportunities for economic growth based on advances in interdisciplinary life sciences.

Grand Challenge 1: Advancing the Bioeconomy: A Blueprint for Wellness

Perhaps the largest contribution of biotechnology and medicine could make in the next decade that could dramatically change the economic landscape is in the area of Wellness. Our current system of developing new medicine and the healthcare delivery system that drives current economic liabilities is entirely based on products and services that address disease and dysfunction. Our R&D pipeline and healthcare delivery is primarily geared toward extending life based on a greater understanding of mechanisms and processes that erode with age or genetic or other defects in health introduced by altered growth (cancer) or metabolic (diabetes) mechanisms.

In these endeavors we have learned considerably new information on background status of health across the living complexity from cells, tissues, organs, and animal and human systems. One large contributing factor to these advances has been systems biology tools applied to nutritional inputs to living systems across scale. An example of these advances is the current studies in natural products and their effects on wellness across living scales. Flavinoids such as resveratrol or quecertin are two recent examples of natural products that have been evaluated across living scales from the molecular scale to human clinical trials to examine improvements in boosting immunity and cognitive conditions that could contribute to wellness. Both of these natural produces are making their way to the market in as GRAS compounds (generally accepted as safe) and being used by large populations of people as supplements (e.g. Q-chews). These examples also point out the

motivations in both the academic and private sector as we have seen NIH increase its investments in what historically had been termed 'alternative medicine', and corporations like Nestle invest in large clinical trials to determine how nutraceutical applications could be amplified in their increasing interest in 'probiotics'. Early evidence indicates that quecertin can boost immunity and increase antibody titers when taken in conjunction with flu vaccine. Resevretrol trials indicate increased cognitive function following increased administration. Only a handful of venture firms have focused on wellness. Pioneer examples include Burrill Ventures that has invested in products that increase satiety (or the feeling of fullness), natural sleep aids, probiotics and food products that improve heart health. These trailblazing efforts in biotechnology start-ups have yet to yield significant results primarily because of the challenges in changing consumer behavior and the evidentiary base of science behind product claims.

These examples are brought forward not to promote these products as ready for large scale promotion in wellness treatments, but rather to point out that opportunities to leverage gains in knowledge creation around wellness are ripe and could have broad impact.

Incentivizing Wellness Behavior

It is asserted here that stimulating investments in wellness in the academic and industrial sectors could have profound impact on new knowledge products available for translation into new medicinal practices that could change the paradigm of future medicine dramatically reducing the cost of healthcare delivery. Yet, to ultimately be successful, wellness investments in science and technology development will require change in behavior. The dramatic rise in healthcare costs in this country are driven by people not making educated health decisions during their lifetime. The ability to incent good health behavior and focused wellness decisions will require innovative programs and leadership to drive these innovations into practice.

One proposal offered here would link changing wellness behavior to individual economic incentives. The Progressive Auto Insurance Company has a new program that monitors driver performance in real time and links performance to premiums paid by individual customers. People can decide to drive the within the speed limit or avoid more dangerous driving behavior and reduce their auto insurance premium. Safeway established precedence for a similar strategy in changing individual wellness behavior by linking use of health club facilities to reduced health insurance premiums by employees. Safeway also enjoyed a 30% reduction in healthcare delivery costs as a result of this program. These two examples from two different sectors demonstrates the power of linking changing behaviors to economic incentives.

Consideration of novel additional incentives to promote wellness behavior should be considered. Tying nutritional health and individual weight loss to income tax incentives and insurance premiums could provide a novel way for individuals to actively participate in wellness. Tax incentives for participating in health, wellness, and exercise programs through tax deductions or direct rebates based on confirmed health status. Corporations that are burdened with high healthcare costs should also be incentivized to participate in programs through corporate tax benefits for offering their employees programs that would promote wellness. These programs should extend beyond wellness visits and become more direct in incentivizing weight loss and good health decisions (e.g. smoking cessation).

Stimulating research and development opportunities in wellness should be considered. These include launching new initiatives across academia and federal laboratory system. The use of University Associated Research Centers (UARCs), multi-university research initiatives (MURI) and public private parternships should be used to establish this grand challenge. The DoD operates the largest healthcare system in the world (Tricare) and could be used to explore the intersection of reducing healthcare cost delivery and emerging discovery and technology from these efforts.

Specific Recommendations for Advancing The Wellness Blueprint for a National Bioeconomy.

- Increase federal research and development programs specifically geared toward wellness. Include aspects of nutrition, immune enhancement, and cognitive health. Utilize UARCs, MURIs and public private parterships to stimulate knowledge products in wellness
- Encourage state sponsored loan programs to small business and start up biotechnology companies pursuing products and services in wellness
- Expand education and advertising programs in wellness through consumer product labeling and increased STEM activities directed at good health practices
- Tie economic incentives for individual behavioral changes tied directly to wellness programs including tax credits, rebates, and deductions for participating in nutrition and weight loss programs, physical exercise and smoking cessation programs.

Grand Challenge 2: The Walk Again Project

Many futurists have declared this century the century of the brain. We have made enormous strides in our understanding of information stored and transmitted by the brain in spite of having a fundamental theory for how the brain codes and processes information. Yet, we are poised with an opportunity utilize recent advances in brain assisted devices to create what some would call 'biblical' changes in peoples lives. The cochlear implant that enables the deaf to hear is a powerful example of what can be achieved. Similar efforts are underway with retinal implants to enable the blind to recover sight. The walk again project is a grand challenge that recognizes this potential for stimulating the bioeconomy and mirrors the challenge John Kennedy to our nation that inspired so many people and established the US blueprint for science and technology of that era.

We are poised to launch a new era of brain technology that will have as dramatic an impact on US science and economy as a man walking on the moon. The impact of translating brain science into useful areas of economic impact is driven by the wide application space including learning, entertainment, and in enhanced human performance. In this latter area, the walk again project is an exemplar of the possible, and will crystallize the same power of asking our country to consider a man walking on the moon. The walk again project will challenge our country through public and private sector efforts in brain science and technology to establish the ability of those disabled to walk again on the earth. In doing so, it will stimulate wide investments in new devices that impact multiple areas of economic impact.

We have had the ability to image regions of the brain and denote areas of metabolic activity associated with specific brain functions and dysfunction. In addition, in the last decade new tools have been developed that enable the direct measurement of ensemble of neurons. These new devices enable direct measures of large areas of information coding in the brain from tens to thousands measured simultaneously in real time. This orchestra of neuronal activity has been the subject of recent intense activity in the neuroscience and neurotechnology community and has enabled the grand challenge posed here…..to enable those with lost motor function (quadraplegics, paraplegics, and those that lost limbs to landmines and in military operations) the ability to recover normal mobile function and walk again.

This vision has its roots at DARPA at the turn of this century where the first studies to demonstrate the ability of non-human primates to move objects on a computer were demonstrated at Duke University. That historical "Aurora" project program has advanced to build a prosthetic arm that emulates the high degree of freedom mobility of a real arm. Yet, the ability to interface the complexity of brain signals to these devices is lacking. This grand challenge would create a novel set of devices that would enable for the first time, the extraction of useful brain information for recovering motor functions. This would unlock a trove of useful information and devices that could extend into a number of devices for enhanced communication,

entertainment and learning. Device development would include implantable and non-invasive wearable devices combined with new robotics and prosthetics that result in the recovery of motor functions in different patient populations (military and civilian) including victims of landmines or improvised explosive devices, car accidents, or other motor dysfunctions. This grand challenge would also expand our understanding of brain function and could lead to other developments in neurotechnology. Over the last decade we have seen an expansion of brain devices and their impact in areas such as Parkinson's Disease. Direct brain stimulation is now also being examined in Alzheimer's and other cognitive deficits and mood disorders. With the advent of non-invasive means to extract signals there is great potential to expand applications into communications, learning, and entertainment. The emergence of increasing personal communication and learning devices and entertainment systems that rely on multimedia presentations, this area is rich for economic future impact resulting from translational research and development

This opportunity has been recognized in the global science and technology community. The European commission has recently released a grand challenge project focused on unlocking information in the brain with its center at EPFL Lausanne. This 500 million euro effort spans across Europe and will seek to extract useful brain science and technology over the next 5 years into realizable gains in the public and private sector. The Brazilian government has set a similar grand challenge that combines advances in neuroscience and technology with an educational mission and to enable a paraplegic to walk into the opening ceremony of Olympic stadium in 2016 using a brain assisted device (such as a prosthetic or exoskeleton). The proposed walk again grand challenge would put the US on the global stage of brain competitiveness. This global community also presents a great opportunity to build partnerships in this key area of future growth and potential for mankind.

Specific Recommendations for Advancing A Blueprint for A National Brain Bioeconomy:

- **Establish a Walk Again Grand Challenge project that exploits recent advancements in brain science and technology and sets specific goals for human performance enhancements**
- **Establish public private consortia and research and development institutes that promote discoveries and commercial development of brain assisted devices that can be applied across learning, entertainment, and health applications**
- **Establish an office within NSF, DoD, DoE, and HHS that direct federal investments in Neurotechnology Efforts to promote and execute this grand challenge and related efforts.**
- **Define workforce development and STEM programs in industry and academia to promote neurotechnology**

- **Leverage the US Walk Again Grand Challenge in the Global science and technology community**

Grand Challenge 3: Creating a Bio-based Defense Industrial Base

One of greatest future challenges is to 'rightsize' our defense budget to align with current and future threats. While the current fiscal climate has created an acute process by which the defense department will see cuts, the strategic alignment of defense expenditures with areas that will contribute to mitigating these threats as well as contribute to a blueprint for a national bioeconomy is needed.

Large expenditures in Biodefense and traumatic brain injury are not sufficient. The current approach in investing in biodefense by the defense department has yielded limited results. This has as much to do with the approach as with the contracting and administration of the programs. Directed efforts at acquisition reform and contracting rules are needed if the large defense and federal investments in biodefense and biotechnology are to be realized.

The current expenditures in defense aligned with life sciences and biotechnology also dramatically underestimate the potential for how defense investments could contribute to a bioeconomy much the way our current GDP in defense contributes. We need to establish a new military industrial base that recognizes the potential for life sciences and biotechnology to contribute to the national bioeconomy.

There are ample opportunities in biodesign of materials and new systems that could provide a strong foundation for building and realizing this vision. We have seen microcosms of potential such as the defense investments in force dynamics of winged flight and legged locomotion that have turned into new microair vehicles being developed for military applications in autonomous sensing, decontamination and reconnaissance. Others examples include the bigdog robot that was YouTube's most watched video in 2009 (over 11 million hits). This robot employs simple force dynamic principles of legs and captured the imagination of the public in profound ways. New materials base on gecko feet, infrared and chemical detection from insects, and new production methods utilizing plants are just a few examples of opportunities for defense-based science to emerge as real technology solutions to defense and non-defense problems. Yet, we do not have a concerted well-defined industrial base to support these efforts. We need a concerted effort to develop a broad base of science, technology opportunities and biological products that can contribute to national security. We need a "Bio Boeing".

Essential to these efforts will be to recognize that cost must be a design feature that drives their development. We can no longer support the model that builds high cost defense specific platforms and expect the US economy to support the development.

Specific Recommendations for Advancing a Blueprint for a National Bioeconomy Through a Defense Industrial Base

- **Establish a National BioDesign Institute to exploit advances in Defense investments in biological products for medical and non-medical applications**
- **Launch specific graduate and post-doctoral fellowship programs to recruit and nurture a new workforce dedicated to building a Biobased Industrial Base**
- **Examine acquisition and contract reforms to create flexibility and agility in facilitating growth of a Biotechnology Defense Industrial Base**

The Role of Two-Year Colleges in Providing and Developing an Educated and Highly Competitive Bioeconomy Workforce

Andreas Heltzel (Ph.D.), Amanda Latimer (M.Sc.), Brent Beall (Ph.D.),
Jeff Rapp (Ph.D.), Margaret Chambers (Ph.D., DVM) and Michael Mouat (Ph.D.)

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The competitiveness and productivity of the bioeconomy industry in the US relies greatly on a large workforce pool of highly educated and professionally trained technicians and other such support personnel. Technically skilled personnel represent, by far, the largest part of the private-sector workforce foundation. Technicians are responsible for the crucial bench-level implementation of biological research innovations to be commercialized by the private-sector bioeconomy.

The development of a competitive technical bioeconomy workforce is dependent on life sciences programs offered by four-year universities and two-year academic facilities including traditional community colleges as well as colleges for the community such as technical colleges.

Four-year academic programs in the life sciences generally address biotechnology laboratory skills on a more theoretical level. In contrast, two-year colleges offering life sciences programs specializing in understanding, acquiring and actively mastering biotechnology laboratory and related scientific skills provide a very focused approach, training a large number of educated life sciences technicians. Accordingly, two-year biotechnology facilities are more efficient and time- and cost-effective for the students and for the life sciences industry in producing a workforce ready to transition directly into the private-sector bioeconomy.

The success of developing a competent bioworkforce advanced by two-year colleges offering appropriate biotechnology programs relies on close cooperative relationships between local colleges and regional life sciences businesses. Specifically, academic training should complement ever changing business expectations and needs such that students can successfully transition from two-year college graduation into biobusiness employment. Two-year biotechnology college programs are perfectly positioned to team up continuously with local biotechnology businesses when developing academic learning and laboratory skills outcomes. Close collaboration of this kind between two-year academic facilities and the life sciences industry is not easily feasible involving a four-year university due to differences in academic flexibilities and missions.

In order for competitively staffed and equipped two-year biotechnology programs to succeed in producing this significant portion of the bioeconomy workforce, the academic learning and training effort must be accompanied and supported by:

- An effective outreach program between local high schools and colleges, channeling prospective high school graduates into a two-year biotechnology program;
- Collaboration agreements and establishment of liaison teams continuously linking academics and biobusiness entities defining strategic academic and job training goals;
- A funded student internship program in a local biobusiness, bridging college academics and biotechnology business experiences.

The successful mission of a two-year biotechnology program depends on Federal funding allowing the realization of large and effective biotechnology job training programs. Furthermore, a Federal grant program for two-year biotechnology programs must be created that specifically addresses the herein described funding needs of such academic facilities involved in training and boosting the nation's bioeconomy workforce.

Federal funding of academic outreach and collaborative academic-business agreements need to be persistent and sustaining to have a long lasting impact on the creation of a competitive bioeconomy workforce. Likewise, a public-private funding partnership initiative must be in place to fund an internship stipend program allowing financially disadvantaged and other students during their last academic term to work and gain valuable and significant real-time experiences in a biotechnology business.

In summary, the role of technical colleges offering biotechnology programs is to produce increased numbers of highly educated graduates in the life sciences enhancing the national bioeconomy workforce by supplying highly competent technicians. Therefore, two-year colleges promote the nation's efforts to boost its economic and educational competitiveness worldwide addressing 21st century global challenges in health, energy, food production and the environment.

Recommendations for Building a 21st Century BioEconomy

From the Small Biotechnology Business Coalition

December 6, 2011

INTRODUCTION

This set of recommendations is in response to the October 11, 2011 Request for Information (RFI) from the White House Office of Science and Technology Policy (OSTP) titled *Building a 21st Century Bioeconomy*. The stated purpose of the RFI is "to solicit input from all interested parties regarding recommendations for harnessing biological research innovations to meet national challenges in health, food, energy, and the environment while creating high-wage, high-skill jobs."

The Small Biotechnology Business Coalition (SBBC) is the leading advocacy voice for the over 2,000 independently owned, U.S. based small biotechnology and medical device firms.[1] All SBBC members were provided with drafts of this document and 10 to 15 company representatives elected to contribute ideas or input.

Cognizant of the fiscal constraints facing the U.S. government at this time, **none of the following recommendations require new government spending.** At most they would require small shifts in funding from programs that are generally delivering less economic value. Furthermore, we believe that **most of these recommendations can be immediately implemented without the need for new legislation**. To the extent that any of these ideas require some legislation these would not require an appropriation and would likely garner bipartisan support.

RESPONSES TO SELECT REQUESTS FOR INFORMATION

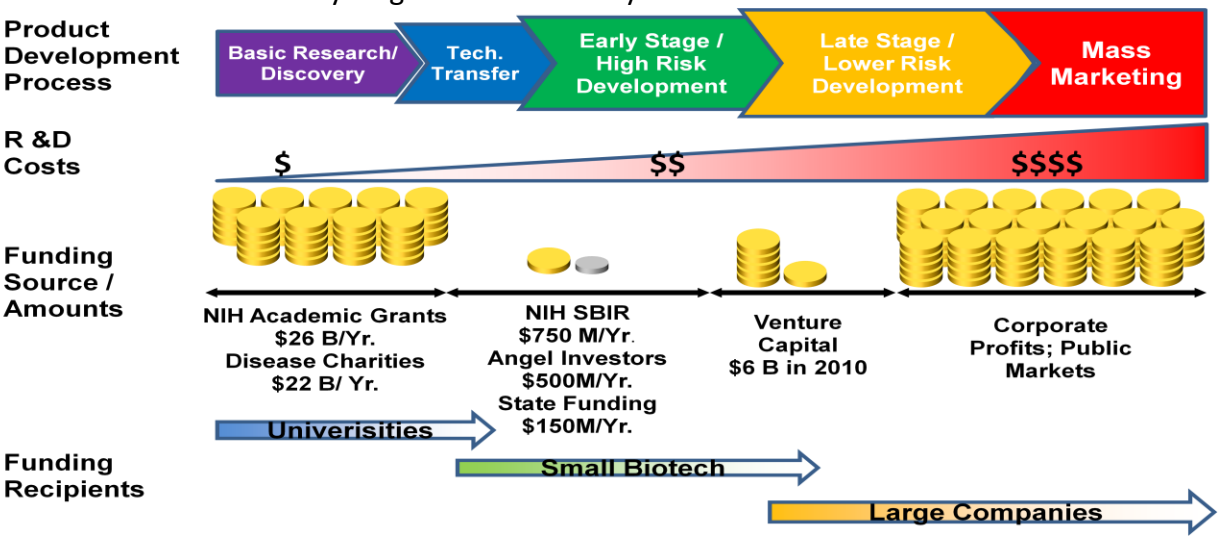
What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both. (Q5)

The single greatest barrier to moving biological research discoveries from the lab to commercial markets is lack of necessary funding. In the current funding environment in which investors and large corporations are reluctant to fund anything new, small biotechs are mostly reliant on the NIH SBIR program to commercialize promising

[1] www.SmallBiotechCoalition.org; Tel. 301-917-6538

technologies developed by academic researchers. However, nearly all of the ~$30 billion received by the NIH each year goes to hypothesis driven basic research by academics. While this research sometimes serves as a foundation for future clinical and commercial applications, NIH funding almost always ends long before private investors and corporations will commit to funding their commercialization. Furthermore, as the following diagram illustrates, the amount of funding available for basic research dramatically outweighs that available for the translation of early stage research into clinically useful products.

It is very difficult for small companies to find investors willing to absorb the substantial risks associated with early stage research. Policy makers need to be aware that the



amount of available private risk capital pales in comparison to the amount of public money invested in life science research.

More than 90% of small biotech companies in the U.S. today fund their R&D through a combination SBIR grants, state grants, and individual "Angel" investors. (Institutional venture capital is invested in well under 10% of companies, and these firms are disproportionately based in the San Francisco or Boston regions.) **Thus, basic / discovery life science research by universities receives about $50 billion per year in grants (NIH and philanthropy) while only about $1.5 billion is available to the 2,000 U.S. small biotech companies to translate this research into commercial products.**

The SBBC recommends the following specific initiatives to remedy the significant funding imbalance between basic and applied research as illustrated above. Importantly, each of these recommendations could be implemented by the Executive branch without new legislation or appropriation.

A. Allocate funds for a new NIH "Translational Research /Technology Transfer" award mechanism

Outside of the SBIR allocation, the NIH provides almost no funding directed at reproducing, validating, or expanding the research results of academic investigators so as to reduce the risk, costs and timelines associated with translating basic research into clinically useful and marketable products.

This urgent problem was described in a front page report in the *Wall Street Journal* only last week. According to the report, the vast majority of NIH funded research that is published in academic journals cannot be repeated or reproduced thereby leading pharmaceutical companies to waste large sums of money in clinical studies that fail. Smaller companies, in particular, especially suffer when we are required to invest considerable time and money attempting to develop products and technologies based on academic research which was either inherently flawed or insufficiently developed before being transferred to our companies.

The commercialization success rate small biotech would significantly improve and accelerate if the technologies that they are developing could be further advanced before they deploy significant private capital. To that end **SBBC recommends that no less than 15% of the NIH's extramural budget should be allocated to a new Translational Research / Technology Transfer (TRTT) contract or grant program**. Applicants for TRTT contracts would mainly be academic institutions seeking to replicate, expand, or validate their or their peers' RO1 grants results. Small businesses that have partnerships or licenses from universities could also compete for TRTT awards. Priority would be given to applicants with licenses or option agreements with companies that agree to take over funding after certain technical milestones are achieved. The size of award would range from $500,000 to $1 million per year over three years.

A related program could be implemented for the NIH's Intramural research program. Such an incentive is particularly needed since enthusiasm for CRADAs and other industrial collaborations by the intramural community has been dampened in recent years due to increased scrutiny of such relationships by NIH ethics authorities.

B. Create a new pilot "expert review" system for TRTT and SBIR awards

Peer review is a cornerstone of the NIH grants system and is ideal for hypothesis driven research, scientific publications and honors and prizes. However, it is less than ideal for advancing technologies towards commercialization. For these reasons agencies like the Defense Department and NASA use expert review rather than peer review in evaluating proposals for external for funding. Topics of interest to academic scientists often differ from the needs and priorities of patients, physicians or the commercial marketplace.

Under an expert review system, NIH program managers with relevant experience or training, aided by outside experts (physicians, patient advocates,) would play a key role in funding determinations. Continued funding would depend on the achievement of

technical milestones. Importantly, awardees could get feedback from the program officers before submitting an application and could negotiate technical milestones as the R&D progresses. Within a given topic area funds could be redirected from awardees who are not achieving their milestones towards groups having more success.

The NIH should experiment with an expert review system for its SBIR program and other applied and translational grants and contracts. Feedback from all stakeholders should be solicited before the pilot is made permanent.

What specific changes to Federal Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally funded bioeconomy related research? (Q6)

A. Adopt a more commercial (rather than academic) review process for the NIH SBIR program

NIH's extramural funding is directed largely towards basic academic research, and the Center for Scientific Review draws heavily from their research grant recipients in the academic research community for reviewers. Review panels thus tend to reflect the basic research focus of much of NIH's extramural research. SBBC member companies often find that reviewers of their NIH SBIR proposals undervalue product innovation, rejecting proposals with high probabilities of commercial successes merely because they find the basic research underpinning the technology is insufficiently innovative. Since NIH's standard procedure is to have only one or at most two reviewers thoroughly examine each proposal, who then present their findings to the full group of reviewers, the product innovation element that is so critical for commercial success can be substantially undervalued.

- The NIH should explore the aforementioned "expert review" process for its SBIR program. This would bring the NIH SBIR program in line with the SBIR program at the National Science Foundation (NSF) wherein Program Officers actively group the triaged grant applications by technical subject matter, select appropriate technical and business subject matter experts as reviewers, and then join the review committee to guide the review process. Permitting Program Officers to participate in the review process would add speed and predictability to the review process and permit more useful interaction between the applicant and the SBIR program staff. For example, companies could ascertain their likelihood of success before investing the time of preparing a full grant application. The NIH model of providing a "Chinese wall" between the reviewers and program staff is useful only in an academic context.

- The aforementioned review system should first be implemented on a pilot basis and should provide safeguards to prevent domination of the review process by Program Managers.
- The NIH should follow the lead of the NCI SBIR program in hiring SBIR Program Manager with industry experience.
- The NIH should accelerate its efforts to recruit grant and contract reviewers with a combination of technical and business backgrounds, including representatives from small and large companies and venture capital firms. (The National Cancer Institute (NCI) SBIR program has recently been successful in this regard, particularly for their Phase II Bridge Award program.)
- In order to help recruit qualified reviewers from small business, consideration should be given to compensating companies that make available their personnel for this purpose. This could be structured, for example, as a small supplement to existing SBIR grants.
- Make clear to the reviewers that "innovation" for purposes of SBIR can refer to the product or technology being developed, not necessarily the research per se. Frequently research plans directed to routine but essential tasks (e.g. optimization, validation, toxicology testing, animal trials, etc.) are deemed "not innovative" even thought the product being developed is highly novel and unique. This results from reviewers improperly applying academic criteria when reviewing SBIR grants.

B. Shorten review and award cycle timelines

Currently, the NIH review/award process takes 8-9 months from proposal submission for work to commence. It is recommended that NIH condense the time frame for its SBIR reviews. We would suggest the use of the DoD SBIR process as a model as it has a shorter time frame, 4 months—half of NIH.

C. Create and expand programs to transition NIH SBIR funded technologies to the marketplace

SBBC members believe that the NIH lags behind other agencies such as DOD and DOE with respect to programs which help transition SBIR funded technologies into the marketplace. The following programs would help SBIR grantees transition to product launch or otherwise attract private investments and corporate partnerships.

1. Expand the NCI SBIR Phase II Bridge Award program

In 2009 the National Cancer Institute (NCI) began a pilot program called the SBIR Phase II Bridge Award program. Modeled after NSF's "Phase IIB Option," this is a three year, milestone driven grant (up to $1 million per year for three years) that requires matching

funding from private investors (Angels or VCs) or larger companies. Importantly, the reviewers for the Bridge Program came primarily from large pharmaceutical companies, venture capital firms, and successful small companies.

To help facilitate investments and partnerships for the Bridge Program the NCI SBIR staff hold an annual investor forum and are planning other initiatives in this regard.

SBBC members are enthusiastic about this pilot program and recommend that it be made permanent and be adopted by other Institutes at the NIH. However, if Congress amends the SBIR statute to permit companies majority owned by venture capital firms, it is important that the NIH provide safeguards to ensure the Bridge Program does not become dominated by the VC community. It is important that companies with smaller investments from Angels not be displaced. Also it is important that significant flexibility be according to investments from a variety of sources and input from small companies be given weight in structuring the rules for investment eligibility.

2. Create and implement a new NIH Phase III acquisition program

SBIR Phase III generally refers to the commercialization of SBIR funded research or technology using funds other than the SBIR Program. This can include federal funding (outside of the SBIR set aside) or private sector funding. The Departments of Defense and Energy have highly successful SBIR Phase III programs.

The NIH has historically avoided a formal Phase III program based on the premise that unlike DOD and DOE the NIH does not represent the end user or customer. This premise should be reconsidered. Public and private sector end users (large companies, research institutes, etc.) could be brought into the SBIR contract program in Phase I with the goal of eventually acquiring the product or intellectual property after successful Phase II development.

The SBBC recommends that NIH should develop a Phase III program along lines herein outlined.

i. *NIH Acquisitions*

Under a public sector Phase III program, the NIH Intramural Program could specify particular technologies or products that they need and participate in Phase I and Phase II SBIR contract reviews. The expectation is that following successful Phase II development those entities would purchase products from the company, who would also be free to sell the products to others. This program would likely work best for research tools, medical devices, and other products that do not require expensive clinical trials before they can be commercialized, but could also include supply of clinical trial materials.

EXAMPLES:

- The National Institute of Neurological Disorders and Stroke (NINDS) Intramural Program seeking the development novel animal models for Parkinson's disease research and drug testing.
- The NIH Clinical Center seeking innovative imaging software for analysis of tissue sections by their anatomic pathology lab.

ii. ***Private Sector Acquisitions***

A private sector Phase III program would involve large companies seeking innovative technologies that (i) meet a compelling unmet public health need and (ii) would be too risky for them to develop independently. These companies would assist in crafting SBIR contract RFPs and would have their R&D managers serve on review committees. The expectation is that following successful Phase II development those entities would enter co-development or license agreements with the SBIR firms (who would also be free to negotiate with others). This program would likely work best for novel therapeutics and diagnostics that require expensive clinical trials before they can be commercialized. In one implementation of this recommendation, the NIH would serve in a brokering capacity bringing together the SBIR entity with the private sector entity looking for a particular product/device/etc. Universities have these types of units to bring together faculty and companies or faculty companies with outside companies to partner on projects.

EXAMPLES:

- Pfizer seeking the development of new drugs for treating various autoimmune diseases.
- Roche Diagnostics seeking validated biomarkers for predicting lung tumor response to targeted therapies.

D. Increase the NIH SBIR/STTR allocation over three years

In light of the economic downturn, the SBBC strongly recommends a three-year increase in the percentage of NIH grants allocated under SBIR/STTR from the current 2.8% to at least 5.0%. This is justified since companies that successfully bring new products and technologies to market create new jobs that can be sustained without continued government funding. Furthermore, private equity capital has become significantly curtailed, especially for higher risk endeavors like biomedical R&D.

The SBIR statute provides that agencies allocate no less than 2.8% of their external funding to small businesses. This creates a floor, not a ceiling, which can be increased by the Executive branch without legislation.

2010 NIH SBIR applications increased by 40% from the prior year while the number of applications that received funding plummeted to 17.0% from 24.5% in 2009. At the National Cancer Institute 2010 SBIR applications rose by 68% from the previous year. This is likely due to the difficulty in accessing private sources of capital for early stage ventures. Competition is expected to increase substantially with the anticipated participation of companies owned by venture capital firms as a result of pending SBIR legislation.

It also is noteworthy that the European Union's biomedical research authority awards about 15% of their funds to small businesses.

After FY'14 an outside expert review committee could be convened to recommend whether the three year increase should be maintained or the allocation returned to current levels.

E. Create SBIR Advisory Boards

It is urged that each NIH Institute create an SBIR Advisory Board to provide ongoing input on operations and topic priorities. The SBIR Advisory Boards would comprise representatives of successful small and large businesses, disease advocacy organizations, as well as the investment community.

F. Appoint a Deputy Director for Small Business Innovation at the NIH

A new Deputy Director position should be created at the NIH with specific oversight over the SBIR program. While each Institute should maintain independent funding authority, the Deputy Director would seek to implement best practices across institutes and would serve as a primary liaison with various stakeholders including the business community and members of Congress.

What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges? (Q. 8)

The economic downturn has significantly transformed the funding environment for small companies engaged in high risk, high impact R&D. Institutional venture capital has generally moved away from early stage investments leaving individual "Angel" investors to fill this important void. In light of these trends the following initiatives could be implemented by the Obama Administration to create billions of dollars in new investments without any increase in the deficit.

A. Encourage Crowd Funding

As of this writing, legislation to make it easier for companies to promote themselves for small investments (under $10,000) from individual "Angel" investors is advancing through Congress. If enacted the Administration could help encourage "crowdfunding" by maintaining and promoting an SBA database of SBIR grantees who are seeking equity investments to advance their SBIR funded technologies. This website InvestAmerica.gov would be organized by technical fields and disease areas so that prospective investors interested in advancing cures to particular diseases can identify relevant companies.

B. Redirect Pharmaceutical Settlements to Small Biotech Companies

Merck & Co. recently agreed to pay $950 million to resolve government allegations that they illegally promoted Vioxx and deceived the FDA about the drug's safety. GlaxoSmitKline recently agreed to pay $3 billion to settle U.S. allegations of improper drug marketing. Pfizer, Eli Lilly and AstraZeneca have also entered expensive settlements with the federal government in recent years.

The Administration might permit these companies to reduce at least part of their settlement obligations if they invest an equal or greater amount in NIH SBIR grantees seeking corporate matching funds as part of their Bridge Program. Helping us bring our products to market faster gives the taxpayers a return on SBIR investments already made thereby creating far more economic activity that blanket payments into the U.S. Treasury.

Alternatively these settlement funds could be pooled into a common fund to supplement SBIR grants. The drug companies could offer advisors to the fund in more arms length manner.

What specific improvements in the regulatory process for drugs, diagnostics, medical devices, and agriculture biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges? (Q. 15)

A. Implement progressive, staged approval for drugs, devices, and diagnostics developed by small companies

The burdens of regulation fall disproportionately hard on small companies which are responsible for the bulk of innovative products. The FDA should initiate an array of provisional approval processes to permit the marketing of products proven safe but for which efficacy data is promising but not yet conclusively proven. Post market surveillance data could be incorporated into subsequent assessments of the risks vs.

benefit of continued marketing of the product. This model is generally analogous the CMS' Coverage with Evidence Development initiative (below).

The SBBC formed a Diagnostics Working Group that met with the FDA Office of In-Vitro Diagnostics in September 2010 in connection with their anticipated regulations of Laboratory Developed Tests (LDTs). We submitted a formal proposal to the FDA (available on www.regulations.gov or the SBBC website www.smallbiotech.org) in August 2010 that seeks a limited "provisional PMA" for small companies to permit them to "test the waters" by selling their tests to up to a limited number of patients per year. Patient protections are included in the proposal.

B. Expand Medicare Coverage with Evidence Development (CED)

Timely reimbursement is essential for innovative small biotech companies and our investors but we face steep hurdles and long timelines before receiving national or even local coverage determination from Medicare. CMS's "Coverage with Evidence Development (CED)" program provides an ideal way to permit innovative small companies to launch their products and earn revenues while collecting additional data supporting the clinical value of our products. CED is particularly useful for medical device and diagnostics products which can often be launched by small companies before obtaining venture capital or large company partnerships. Since our companies typically lack resources for a national sales force and marketing campaign, local CED reimbursement from Medicare contractors should permit our companies to test market our products in a few states before a national roll out. Accordingly we urge the Administration to promote CED among its Medicare contractors for innovative products developed by small companies.

C. Accelerate the FDA Orphan Products Grant Program with Vouchers.

Small biotech companies often lead the development efforts for treatments of rare diseases as larger companies typically shy away from smaller market opportunities. The FDAs Orphan Product Grant Program is therefore very important to the companies that SBBC represents. Unfortunately the budget for this program (~$14M) has been nearly flat since 1995 even though the number of grant applications has at least tripled from 30-40 in 2007 to well over 100 in 2010 and 2011.

In 2010 the *Creating Hope Act* was introduced in the Senate to offer "priority review vouchers" to large pharmaceutical companies seeking expedited review for large market drugs if they agree to invest in cures for rare diseases. The Administration should consider implementing a similar program by Executive Order wherein pharmaceutical companies that invest in small companies addressing orphan diseases would be awarded priority review vouchers from the FDA.

D. Promptly promulgate regulations implementing the biologics data exclusivity provisions in the Healthcare Reform Act of 2010.

The Patient Protection and Affordable Care Act contained important provisions giving at least 12 years of post approval exclusivity for biologic products, in order to enable the required investment in product development from a large pharmaceutical company or private investor. Small biotechnology companies believe that the Administration needs to quickly publish regulations on the implementation of this provision in order to help us attract investment.

NATIONAL COALITION FOR FOOD AND AGRICULTURAL RESEARCH

December 6, 2011-by e-mail to bioeconomy@ostp.gov

RE: Comments to OSTP on National Bioeconomy Blueprint

To the Office of Science and Technology Policy (OSTP):

In response to your Request for Information (RFI), the National Coalition for Food and Agricultural Research (National C-FAR) urges you to place a high priority on federal funding for food and agricultural research and education as you carry out your important charge of developing a National Bioeconomy Blueprint.

A vibrant and viable food and agriculture sector is essential to any National Bioeconomy Blueprint. It is hard to conceive of any "bio" initiative that would not have food and agricultural sciences as one of its essential building blocks. This includes a strong commitment to federal funding for food and agricultural research and education. Unfortunately the federal government's track record over the past two decades has been the reverse—flat or declining funding for food and agricultural research and education. Indications are that the nation is not investing enough to develop the science needed translate into productivity increases to feed 9 billion people, let alone provide vital contributions to a bioeconomy.

National C-FAR believes **the nation has a serious deficit in federal funding for food and agricultural science**, just as the nation has a budget deficit. This food and agricultural science funding deficit is serious, long running and unsustainable. Failure to address this research deficit will have real negative consequences, not just to our food and agricultural system but to the entire U.S. economy, and certainly to the effectiveness of any future bioeconomy.

The National Bioeconomy Blueprint represents an exciting opportunity to reverse that harmful trend by embracing a commitment to the increased funds needed to revitalize food and agricultural science. National C-FAR urges OSTP to make this commitment a core principle of the National Bioeconomy Blueprint.

While agriculture is lised in several of the questions posed, it is indeed disappointing to find no mention of food and agricultural science—and no mention of involving the unmatched capabilities offered by the U.S. Department of Agriculture's (USDA) research mission (inter- and intra-mural) in the President's announcement about the series of federal government initiatives being launched as part of the implementation of the America Invents Act. National C-FAR would urge OSTP to remedy this oversight. Much of the focus of the America Invents Act is to streamline the nation's patents process as a way of speeding the translation of new scientific outcomes to the marketplace. However, an investment in food and agricultural science is necessary to create a flow of new scientific outcomes in the pipeline for this process to have the desired results.

National C-FAR would like to offer the following related responses to categories of questions raised in the RFI:

- *Grand Challenges*: Core food and agricultural challenges, such as—feeding 9 billion people, providing nutritious and safe food, achieving global food security, contributing to national energy security through bioenergy, and protecting the nation's natural resources and environment while doing so—should be prominently included among the grand challenges.
- *Research and Development*: Working to achieve these grand challenges will require an increased investment in food and agricultural research and development. Successes will ultimately translate into high quality jobs in rural America and across the nation.
- *Moving Life Sciences from Breakthroughs to Market*: Life sciences are deeply ingrained in food and agricultural science and its multi-faceted missions. But severely constrained, stagnant, constrained funding in food and agricultural life sciences—and necessarily interrelated sciences—severely constrains the pipeline of breakthroughs that present future market opportunities.
- *Workforce Development*: The nation's unmatched land grant system and related research and teaching institutions in food and agriculture are absolutely essential to producing an adequate supply of qualified scientists and technicians to work in agriculture, business and government—and to teach future researchers, and educators. Federal funding is absolutely essential for this system to be viable in the future.

Recent studies have concluded that funding for scientific research for food and agriculture needs to be increased steadily and significantly if future challenges are to be met. For example, in "*Public Agriculture Research Spending and Future U.S. Agricultural Productivity Growth: Scenarios for 2010-2050,*" a USDA Economic Research Service report (EB-17, July 2011) states:

- By 2050, global agricultural demand is projected to grow by 70-100 percent. Meeting this demand from existing agricultural resources will require raising global agricultural total factor productivity (TFP) by a similar level.
- If U.S. public agricultural R&D spending remains constant until 2050, the rate of agricultural TFP growth in the U.S. is projected to decline, with U.S. agricultural output increase by 40 percent by 2050.

Similar conclusions are expressed in "*Investing in a Better Future through Public Agricultural Research,*" (CAST Commentary QTA2011-1, March 14, 2011):

- Publicly funded food and ag research in the U.S. has been essentially flat over the past two decades.
- Public funding of agricultural research in the rest of the world has outpaced investment in the U.S.
- With agricultural research funding delays, productivity increases are expected to slow, and world food prices will rise more rapidly than otherwise projected during the next 40 years.
- Numerous studies find rates of return on public ag research investments of 20 to 80%. Huffman and Evenson (2006) estimate a marginal rate of return of approximately 50%.
- There is an important and necessary role for public research because the private sector faces weak incentives to undertake research in numerous areas of national interest.
- Agricultural research is a low-cost source of future productivity and output increases; but advances in the frontiers of science translate into long lags before benefits are realized, typically 15-20 years.

National C-FAR serves as a forum and a unified voice in support of sustaining and increasing public investment at the national level in food and agricultural research, extension and education. National C-FAR is a nonprofit, nonpartisan, consensus-based and *customer-led* coalition established in 2001 that brings food, agriculture, nutrition, conservation and natural resource organizations together with the food and agriculture research and extension community.

The success of the agriculture and food industry plays a significant role in the overall health and security of the U.S. economy and has been one of the few bright spots in recent years. In 2010, U.S. farms and ranches spent $288 billion to produce goods valued at $369 billion; the value of U.S. food and agriculture exports is expected to be more than $140 billion in 2011, creating a record trade surplus of $42.5 billion. Furthermore, the jobs of 21 million Americans depend on the vitality of the U.S. agriculture and food sector.

The bottom line is simple—commit to increased federal funding for food and agricultural science and education. The National Bioeconomy Blueprint must include as one of its core components a true commitment to significant increases in federal investments for food and agricultural research and education to have a realistic chance of being effective in achieving its goals.

National C-FAR appreciates the opportunity to share its views.

Respectfully Submitted,

R. Thomas Van Arsdall

R. Thomas (Tom) Van Arsdall, Executive Director

[redacted]

ONYX PHARMACEUTICALS

Request for Information: Building a 21st Century Bioeconomy
Office of Science & Technology Policy, The White House
Comments Submitted Electronically to bioeconomy@ostp.gov

Onyx Pharmaceuticals, Inc.
December 6, 2011

Thank you for publishing a request for information to solicit input regarding recommendations for harnessing biological research innovations to meet national challenges in health, food, energy, and the environment while creating high-wage, high-skill jobs. As a manufacturer of innovative therapeutics for cancer, Onyx Pharmaceuticals, Inc. ("Onyx") witnesses first hand the challenges and necessary steps to successfully bring a new, effective product to market. We are excited about the future, and believe that biotechnology companies like Onyx will continue to play a crucial role in researching and developing the kinds of products that extend lives and improve patients' quality of life. Additionally, as one of the highest growth companies in the life sciences, we expect to expand our workforce by 50 to 60% in 2012, creating approximately 250 new jobs. As a result, we understand the importance of stimulating innovation as one of the key growth drivers of the emerging "new" economy. Based on these experiences, Onyx respectfully submits these comments for your consideration as you develop the *National Bioeconomy Blueprint.*

Public-Private Partnerships & Research Funding:

Today, the industry is at a crossroads. The old blockbuster model is waning, and we are moving toward an era of personalized medicine characterized by targeting treatments consistent with an individual's genotype and medical history. This is extremely positive for patients and good for agile companies like Onyx, but this rapidly advancing know-how is changing the entire structure of the industry and the nature of our partnerships and collaborations with public and private organizations. This is not unlike major shifts we have observed in a number of other areas, including defense and national security where we now approach both, with smaller, more targeted, and smarter approaches.

In some ways, the entire innovation paradigm is evolving. Historically, innovators have worked sequentially: basic science labs advance a discovery, and then transfer it to clinical experts who often, in the case of academic laboratories, license the promising technology to an organization with the money and resources to bring the treatment to patients. These handoffs are inefficient, and can slow or break down any time a member of this "innovation chain" bumps into the limit of their experience or expertise. As a result, Onyx believes the next great era of life science partnership will focus on greater integration throughout the discovery and development cycle, so that scientists and academicians performing early research can collaborate earlier and more directly with the organizations whose clear mission it is to make new therapies widely available to patients around the globe.

This kind of collaboration is especially important in an era of declining federal resources, which is requiring all of us to become more efficient and collaborative. Public policy will need to respond to this new paradigm and find even faster ways to enable innovation while keeping patients safe. With this in mind, however, we believe that the NIH will continue to play a key role in our nation's health care landscape, as the proprietor for the nation's science. Although we recognize the need for private industry to do more, particularly in such tough fiscal times, Onyx urges policymakers to support current NIH funding levels to maintiain our economic and innovative competitive edge in life science. The NIH serves as a vital partner to the private sector, without which we cannot do our essential work and funding cuts here would have a devastating impact on innovation for years to come.

An example of one NIH program driving innovation is the Cancer Therapy Evaluation Program (CTEP), whose mission is to improve the lives of cancer patients by finding better ways to treat, control, and cure cancer. CTEP accomplishes this mission by funding an extensive national program of cancer research and by sponsoring clinical trials to evaluate new anti-cancer agents, with a particular emphasis on translational research to elucidate molecular targets and mechanisms of drug effects. CTEP uses a scientific process to accomplish its mission. Promising basic science findings are identified and translated into clinical research, both by identifying new agents for evaluation and by identifying biologic characteristics of tumors that may be clinically exploited.

CTEP attempts to forge collaborations within the broader research community and works extensively with the pharmaceutical/biotechnology industry to effectively develop and advance new cancer treatments. CTEP also seeks to involve outside experts and patients or their advocates in the formulation of research priorities. In the selection of clinical research for National Cancer Institute sponsorship, CTEP attempts to fill critical gaps in the national cancer research effort and to avoid duplication of ongoing private sector efforts. In further efforts to control cancer, active new anticancer agents are made available as rapidly and widely as possible for patients.

Onyx views CTEP as a potentially valuable partner in furthering the medical community's understanding of multiple myeloma, for which Onyx is developing treatments. Currently, African Americans are twice as likely to be diagnosed with myeloma and twice as likely to die from the disease, but the cause of this disparity remains unknown. More research is needed to understand the cause of this disparity and to improve treatments for African American myeloma patients. This is the perfect opportunity for a NIH funded program such as CTEP to partner with industry to improve treatments for African Americans who are disproportionately affected with myeloma. As part of building a blueprint for a bioeconomy, the Office should explore expanding or adding additional public-private partnerships between academia, industry and the government, such as CTEP.

Building an Integrated National Health Database:

An integrated national health database would be a transformational effort with broad benefits across the research and healthcare systems. We are at a point where digital information exists on many aspects of health care: birth, death, disease occurrence, ethnicity, and sometimes environmental and work exposures to health altering agents. An integrated national health database would combine this information into a single source enabling research to address questions including the relationship between disease and environment, such as childhood illnesses, obesity, premature birth, and smoking. Additionally, such a database would allow further exploration into patterns of medication use and capture rare or late side effects not captured during clinical trials.

To develop a database, challenges would need to be addressed including how best to de-identify data so that trends can be analyzed without jeopardizing the confidentiality and privacy of patients and how to best to integrate different data fields and systems. Nearly every database is handled differently, whether they belong to hospitals, pharmaceutical companies, private payers, government health records, etc.

The integration task is enormous, but would be an investment that will pay dividends in the future and one that can leverage much of the work completed by the Office of the National Coordinator for Health Information Technology. Such an effort would tap into the strength that the United States has in informatics and potentially lead to new opportunities for careers and jobs in the computer science and life science informatics.

Regulations Fostering Innovation—Exemptions for Orphan Drugs:

Oftentimes in the case of a rare disease, there is little incentive for a pharmaceutical company to invest in developing a cure. The Orphan Drug Act allows for the FDA Office of Orphan Products Development (OOPD) to give grants to companies that are committed to the development of treatments for rare diseases. OOPD provides incentives for sponsors to develop products for rare diseases and the program has successfully enabled the development and marketing of more than 350 drugs and biologic products for rare diseases since 1983. In contrast, the decade prior to 1983 saw fewer than ten such products come to market. It is estimated that rare diseases affect more than 25 million Americans.

The Orphan Drug Designation program provides orphan status to drugs and biologics that are intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug. Government assistance for orphan drugs is designed to reduce cost and balance the economy-of-scale for the product.

The Patient Protection and Affordable Care Act imposes an annual fee on manufacturers and importers of branded prescription drugs in the U.S. The law establishes an overall aggregate fee ($2.5 billion in 2011, rising to $4.1 billion in 2018 and dropping to $2.8 billion for 2019 and following years), which will be annually apportioned by the Secretary of the Treasury based on

each manufacturer or importer's relevant market share of covered domestic sales of branded prescription drugs. The only drug sales considered are those made to or offered pursuant to coverage under government health care programs (e.g. Medicare Parts D and B, Medicaid, Veteran's health plans, Department of Defense coverage, and TRICARE).

Importantly, the provision includes a specific exemption for orphan drugs: the calculation of drug sales for any given year *excludes* the sale of any drugs for which the manufacturer received an orphan drug tax credit (a "section 45C credit"). On October 3, 2011, the Internal Revenue Bulletin: 2011-40 included a section outlining the Department of Treasury's interpretation of the law establishing the new Branded Prescription Drug Fee. In its interpretation, the agency outlined several exclusions to this exemption, specifically a drug is not considered an orphan drug if:

1. the 45C credit for orphan drugs was allowed, but the manufacturers did not claim the credit,
2. a final assessment or court order disallowed the full section 45C credit taken for the drug, or
3. the drug was allowed a 45C credit, but subsequently, the FDA approved the drug for an indication to treat a disease or condition that is not rare. (Note: the drug may be approved for use in multiple rare or orphan diseases and still qualify for this exemption.)

Public comments encouraged Treasury to classify orphan drugs based on whether the 45C credit was allowed, and not on whether it was claimed. This inconsistency in defining an orphan drug poses many challenges to the industry developing orphan drugs and could hinder innovation. The regulation should be modified to state that being eligible to receive a 45C credit is sufficient in determining orphan drug status. A company's decision to act on that credit depends on numerous factors, and a choice to not claim an allowed credit does not change or otherwise influence whether or not a drug is indicated for the treatment of a rare disease. In developing a blueprint for a bioeconomy, Onyx asks the White House to consider modifying this interpretation of the classification of an orphan drug so that it is consistent across regulations and based on whether or not a drug was eligible for a 45C credit.

Moreover, the temporary regulation issued in October states that the exemption of orphan drugs from the fee will not apply if the drug is later approved by the FDA for a non-orphan use. It states, "if a drug is *ever approved* for an indication other than the treatment of a rare disease or condition for which a section 45C credit was allowed, *whether before, during, or after a section 45C credit was allowed* for the drug, sales of that drug are not considered sales of an orphan drug." The Orphan Drug Designation Program was designed to create an incentive to developing a treatment for a rare disease or condition, and this interpretation potentially undermines the overall goal of the program. Additionally, Onyx believes this is contrary to the drafters' intent, and that if a drug is approved for a non-orphan use, any subsequent orphan designation should qualify the product for the exclusion. To prevent this, Treasury should change its interpretation to mean that the sales of the drug for the orphan disease should be exempt from being included in the calculation of the manufacturer's fee, but the sales of the

drug for non-orphan disease indications should be considered in the fee's calculation. This fair approach would continue to protect and promote the goals of the Orphan Drug Designation Program. This issue has bipartisan support; in April 2011, 12 Members of the House (seven Republicans and five Democrats) wrote to Secretary Geithner on this issue.

Conclusion:

Thank you very much for the opportunity to submit these comments for consideration as you draft a national blueprint to build a bioeconomy. Onyx believes that sustained investment in funding of the NIH, support for public-private partnerships, building an integrated health database, and incentives such as those for the development of orphan drugs, will help drive innovation forward, lead to economic growth and ensure that America retains its leadership position in life science innovation.

American Society of Plant Biologists
Cultivating a better future through plant biology research

December 6, 2011

Building a 21st Century Bioeconomy

The American Society of Plant Biologists (ASPB) is pleased to submit this statement to the Office of Science and Technology Policy in response to its *Request for Information: Building a 21st Century Bioeconomy*. ASPB is an organization of 5,000 professional plant biology researchers, educators, graduate students, and postdoctoral scientists with members in all 50 states. Our mission is to promote the growth and development of plant biology, encourage and communicate research in plant biology, and promote the interests and growth of plant scientists.

Plant biology research is an integral part of the foundation upon which the bioeconomy builds its success. In fact, plant biology research makes numerous fundamental and applied contributions in the areas of domestic fuel security and environmental stewardship; continued and sustainable development of better foods, fabrics, pharmaceuticals, and building materials; and the understanding of basic biological principles that underpin improvements in the health and nutrition of all Americans.

Understanding the importance of these areas and in order to address future challenges, ASPB recently organized the Plant Science Research Summit. With funding from the National Science Foundation (NSF), U.S. Department of Agriculture (USDA), Department of Energy (DOE), and the Howard Hughes Medical Institute, the Summit brought together representatives from across the full spectrum of plant science research to identify critical gaps in our understanding of plant biology that must be filled over the next ten years or more in order to address the grand challenges facing our nation and the planet. It is our hope that the findings from the Summit and other similar events will be taken into consideration when expanding the vision for building the bioeconomy.

Grand Challenges

Despite the fact that foundational plant biology research—the kind of research funded by agencies like NSF, USDA, DOE, and National Institutes of Health (NIH)—underpins vital advances in practical applications in agriculture, health, energy, and the environment, the amount of money invested in understanding the basic function and mechanisms of plants is relatively small. This is especially true when compared with the significant positive impact crop plants have on the nation's economy and in addressing some of our most urgent challenges like food and energy security. Both individual investigator/small group research programs and interdisciplinary integrated research projects are needed to meet these priorities. The Plant Science Research Summit began to detail those grand challenges, including:

(1) doubling crop yield by 2050 with fewer agricultural inputs through advances in molecular plant breeding and biotechnology that harness the power of integrating genomic and phenomic data to advance predictive modeling;
(2) sequencing 1000 plant genomes to better understand plant diversity in addition to revealing novel pathways leading to useful plant compounds, structures, and enhanced nutrition;

(3) advancing genetic engineering with the goal of producing designer plants that develop specialty storage organs as bioreactors for valuable products to aid in harvest and purification of biofuels, medicinal products, and a variety of other agricultural products;
(4) creating an environmentally and economically sustainable United States agricultural system based on a thorough understanding of ecosystem function.

In early 2012, a report from the Plant Science Research Summit will be published. This report will further detail priorities and needs to address the grand challenges that will directly affect the success of the bioeconomy.

Research and Development

The *21st Century Bioeconomy Blueprint* needs to significantly enhance ongoing research and development activities as key drivers of the bioeconomy, job creation, and U.S. industrial and agronomic competitiveness. A range of research programs and initiatives must be pursued, including the foundational research that underpins future technological advances, high-risk research typically bypassed by industry, the applied work that seeks solutions to the country's most pressing challenges, and the initiatives which bring together teams of top investigators to work on problems at the nexus of disciplines. The full potential of the bioeconomy will only be realized through this type of comprehensive approach.

Specifically, programs like USDA's Agriculture and Food Research Initiative (AFRI) and Agricultural Research Service (ARS), DOE's Biological and Environmental Research (BER) and Basic Energy Sciences (BES) programs, and NSF's Plant Genome Research Program (PGRP) allow plant scientists and their collaborators to pursue new discoveries that will lead to an increased food supply, cleaner and more abundant sources of energy, and healthier people across the globe. These programs also form the foundation for industries that drive the nation's economic growth and ensure that the United States remains a global leader in technological innovation.

ASPB encourages due consideration for interdisciplinary research in the *Bioeconomy Blueprint*, as work at the intersection of plant biology and other scientific disciplines lies at the heart of our ability to make game-changing advances in areas of national importance. For example, plant biology is at the center of numerous scientific breakthroughs in the increasingly interdisciplinary world of alternative energy research. Interfaces among plant biology, engineering, chemistry, and physics represent critical frontiers in both basic biofuels research and bioenergy production.

Similarly, with the increase in plant genome sequencing and functional genomics, the integration of plant biology and computer science is essential to our understanding of complex biological systems ranging from single cells to entire ecosystems. Dealing with the "data deluge" is now a universal theme in all of biology. Innovative methods to dramatically compress large data sets and create better interfaces for the retrieval of standardized data through plain-language queries are necessary to maximize usage of the existing data. In addition to improvements in extracting valuable data from the large volumes available, progress needs to be made in connecting the vast amount of gene sequence and expression information to gene function. While it is unlikely in the near future to create a high-throughput system for characterizing individual gene function, further support for the foundational research that has provided a majority of the functional data currently available would continue to build on the existing groundwork. Additionally, the establishment of medium-throughput facilities staffed with a tiered workforce with a range of educational backgrounds to tackle the increasingly challenging functional characterization of gene products would also begin to address this need.

Moving Life Sciences Breakthroughs from Lab to Market

Although fundamental research is the first stage of the nation's bioeconomy, it is essential that policies are established that encourage the transition of laboratory research to the commercial marketplace. Because plant biology plays a key role underpinning the agriculture, energy, and life science industries, ASPB supports mechanisms to ensure the transition of cutting-edge research to the marketplace to fuel economic growth. However, there are significant barriers to bridging the gap between the many promising potential products that emerge from foundational research and their translation into products with tangible societal benefits. For example, if publishing high-profile papers continues to be the measuring stick for success in academic research, translational research will always be of lower priority. Furthermore, moving research to the market place is a time-consuming and nuanced process. While all research may not be directly translated from bench to marketplace, it is important to remember that the incremental advances that arise from foundational research may lead to large conceptual advances that one day will make the leap to the marketplace.

As such, the *Bioeconomy Blueprint* should encourage the development of highly visible mechanisms for the funding of translational research, additional incentives for translational research in academia, and public-private partnerships to bridge the gap between fundamental research and product development. Additional federal support for translational research would provide a pathway to market for promising ideas which otherwise may never leave the lab.

The federal government is and should continue to be an economic catalyst by supporting the high-risk, high-reward research that offers potentially groundbreaking solutions, but is too novel to attract private support. As DOE's Advanced Research Projects Agency-Energy (ARPA-E) has proven, federal support for high-risk proposals can move potentially transformative ideas to a place where they can attract significant private support. Providing additional funding for high-risk proposals to transition research to a point at which it can generate interest from industry, venture capital, or angel investors would be a significant boon to growing the U.S. bioeconomy.

Workforce Development

Current estimates predict a shortfall in the needed scientific and engineering workforce as the demographics of the U.S. workforce continue to change. For example, there is a clear need for additional scientists in the areas of interdisciplinary energy research and plant breeding. ASPB applauds the creation of programs like the USDA National Institute of Food and Agriculture's Fellows program to address this problem. However, given the expected need for additional scientists and engineers who are well-grounded in agricultural research and development activities, ASPB calls for targeted funding of specific programs such as training grants and fellowships. One example is the Integrative Graduate Education and Research Traineeship (IGERT) program at NSF. IGERT successfully fosters the development of novel programs that provide multidisciplinary graduate training. ASPB encourages expansion of the IGERT program and the development of analogous programs at other agencies to train a greater number of innovative science leaders for the future.

ASPB further urges the expansion of NSF's fellowship and career development programs, such as the Postdoctoral Research Fellowships in Biology, the Graduate Research Fellowship (GRF) and the Faculty Early Career Development (CAREER) programs. Such an expansion would provide greater continuity in funding opportunities for the country's most promising early-career scientists. Additionally, such continuity and broader availability of prestigious and well-supported fellowships

may help retain underrepresented groups in the science, technology, engineering, and mathematics (STEM) fields.

In addition to expanded fellowship opportunities, ASPB encourages a revolution in academic training of graduates and undergraduates. Many academic programs currently train graduate students to ultimately become tenure-track faculty members. However, only about a quarter of these graduates will eventually achieve this goal. It is important to focus a portion of the training efforts on translating research into application and inviting students to discover how the private sector operates. A reduced emphasis on coursework may allow more time for student opportunities to explore industry as well as other "alternative" careers in science. For undergraduate education, a shift in focus from simply learning the facts to conceptualizing and exploring the process of science in a student centered environment, along the lines of the NSF's and the American Association for the Advancement of Science's *Vision and Change* project, is needed. These types of alterations in the current training system will produce a better-rounded workforce able to adjust to the ever-advancing atmosphere of the life-sciences.

The foundation for encouraging successful entrepreneurship also lies in education. Curricula should be restructured to be more multidisciplinary in nature and include a blend of science with business. Furthermore, risk taking needs to be embraced in academia. Many feel that a substantial portion of the work in a grant proposal must have already been completed to be assured an award. This creates a cycle where more and more of the available funding is awarded to established faculty continuing to work on informative, yet relatively low-risk research. To encourage entrepreneurship and high-risk research in early career scientists, greater incentives must be instated. Programs like NSF's CREATIV and several of NIH's Common Fund programs represent a much needed step in this direction, yet additional funding opportunities of this nature must be established in the agencies that typically fund research for agriculture and other fundamental research in plant biology.

ASPB also urges the further development of programs aimed at increasing the diversity of the scientific workforce by leveraging professional scientific societies' commitment to providing a professional home for scientists throughout their education and careers and to help promote and sustain broad participation in the sciences.

Reducing Regulatory Barriers to the Bioeconomy

ASPB recognizes the need for common-sense regulatory policies that protect both the producer and the consumer. Regulations should ensure that technology is developed responsibly; they should not smother innovation. Current regulatory cost estimates for releasing a genetically engineered (GE) crop onto the market are on the order of $30 million, even as many investigations into the safety of GE crops have shown no adverse effects. In fact, some GE crops have diminished the environmental burden of agriculture by reducing the need for agricultural inputs. Recent advances in agricultural technology hold the potential to provide nutritious food for millions more people worldwide and provide significant environmental benefits. However, current incentives in industry are focused on "input" traits that are of economic benefit to the producers, rather than "output" traits, such as improved nutritional qualities, that are of interest and value to consumers. Thus, the economic regulatory burden cannot be shouldered alone by academic labs with an interest in improving traits that benefit society. Regulatory reform that encourages innovation while addressing realistic safety issues and economic incentives should be a top priority of the *Bioeconomy Blueprint*, as regulations informed by sound science have an important role in protecting and incentivizing all involved.

Regulations also must remain flexible and keep pace with rapidly occurring technological advances. For example, researchers now can manipulate a plant's individual genes to enhance agriculturally important traits, akin to trait improvement through traditional plant breeding. Yet the regulatory measures for simply altering an endogenous plant gene are equivalent to those governing the introduction of completely foreign genetic material. A tiered system of regulations could be introduced dependent on the level of risk to the environment and consumers.

Although regulations are a necessary component of the innovation ecosystem, the *Bioeconomy Blueprint* should outline regulatory goals that do not inhibit future innovation. A key element of this is not layering new regulations upon old ones to the point at which rules become confused or overly restrictive. Simply put, regulations are important in creating an atmosphere which benefits both consumers and producers, but they should not be so cumbersome they stunt future economic growth.

Conclusion

Basic research is vital to underpinning, maintaining, and growing the nation's bioeconomy. Moreover, plant biology research forms the foundation for numerous technology developments that Americans utilize and benefit from every day. Given the current economic environment, it is more important than ever to support scientific research that will facilitate revolutionary breakthroughs in producing nutritious foods, providing sustainable energy, developing new medicines, and protecting our environment, as research in these areas will spur economic growth and job creation. We thank you for your attention and we stand ready to offer continued support for this urgent and compelling vision for the future.

To: Dr. John P. Holdren, Director
White House Office of Science & Technology Policy
Bioeconomy Project Team

Re: Request for Information: Building a 21st Century Bioeconomy

Dear Dr. Holdren and Bioeconomy Project Team: Submitted via e-mail December 6, 2011

We are pleased to submit the following comments in response to the Notice by the White House Office of Science and Technology Policy (OSTP) published in the Federal Register on 10/07/2011, requesting public inputs to identify and propose solutions to the grand challenges facing America in building and sustaining a vibrant Bioeconomy.

OPPORTUNITY

We believe the biggest of the grand challenges currently facing America's Bioeconomy is not scientific. The greatest, most solvable, grand challenge is: To improve the financing of translational science.

Funding is the commitment of money to develop products. Financing is the delivery of money. Funding is and will be constrained in today's tight economic times. However, all the tools and networks already exist to make the delivery of federal funds much more effective. America must do this now.

More efficiency in delivering government funding is the key catalyst for Bioeconomy innovation. Currently, government funding is not aligned to support the promise or the pace of 21st century translational science. The translational science pathway is horizontal and continuous, with a sequence of clearly defined stages to move products directly toward approval, or down selection for science failure.

Government science funding is vertically siloed among different agencies, and is delayed by interruptions between the agency funding cycles. This funding system lacks the product focus and strategic continuity to ensure that basic research is translated efficiently into approved products. Government funding is also hindered by administrative burdens which make Government-funded research take longer than commercial science. These factors discourage private sector investment, cause or contribute to significant research delays and unrealized opportunities for innovation, increase cost, and prevent the nation from fully benefiting from our remarkable scientific enterprise.

The National Bioeconomy Blueprint is THE unique opportunity to identify, highlight, and deploy tools to align the funding and financing paths with the science development path -- and vastly accelerate bioproduct delivery.

APPROACH: 21st CENTURY BIOECONOMY FINANCING

The United States of America must systematically use 21st century financing tools and networks to immediately and practically accelerate translational science. This will speed up bioproduct delivery and enable exponential growth in jobs and investment across the Bioeconomy.

The alignment of funding, financing and science can readily be achieved under existing federal R&D authorities used as a 21st Century Bioeconomy Toolkit. This includes:

- Pledges of grant and contract funds as debt service for Revenue Bond Financing
- Commercial contracts using Other Transaction Authorities
- Advance Contingent Purchase Commitments for high-priority products
- Additional federal funding acceleration authorities
- Financing Partnership Networks

The federal government has deployed these tools for decades to support large-scale projects including construction of research facilities, housing, economic development, and advanced defense science and

technology. Together these tools can transform the bioeconomy by ensuring that a 21st century financing system is in place to accelerate 21st century science.

IMPLEMENTATION

1. **Revenue Bond Financing** is a well-established financing tool used to speed the creation of high-priority public goods with multiple, complex development stages. Funding pledges are converted to up-front cash via bonds, and the bonds are then paid down over time. This tool is used when the benefits of acceleration (faster product availability, faster economic growth) are larger than the cost of financing.

   Taxable revenue bond financing can be applied to translational R&D as follows:
   - Government agencies which are funding the development of high-priority bioproducts convert a portion of existing grant and contract funding to cash tranches and commit the tranches to pay debt service covering the principal and interest on taxable revenue bonds
   - State and local economic development authorities issue taxable revenue bonds backed by these commitments, and distribute the proceeds to companies with federally funded projects based in their areas
   - Companies developing the high-priority products receive the bond proceeds and conduct science using commercial contracts
   - Government agencies establish and validate achievement of science milestones, Technology Readiness Levels (TRL's), performance standards, and company performance sureties
   - Funds from Government agencies with varied funding missions can be aligned and precommitted to fund R&D stages in a linked path to product approval, tied to science milestones rather than diverse, un-aligned agency administrative requirements
   - Private debt and equity capital can be combined with federal funds in capital stacks to fully finance priority bioproducts to licensure and market availability
   - Bioproduct manufacturing in America can readily be financed by taxable revenue bonds issued by economic development agencies

   The Government can and should immediately set up standardized bond financing vehicles – Innovation Bonds – to speed the translation of science into bioproducts.

2. **Other Transaction Authorities** (OTA) are well-established Government contracting vehicles for R&D. They allow flexible commercial contracts and reduce administrative burden. The Government can and should immediately make OTA's a standard contract vehicle for Bioeconomy translational science.

3. **Advance Contingent Purchase Commitments** are binding Government acquisition contracts, conditioned on successful product approval, for the purchase of high-priority products in development. Advance contingent purchase commitments provide early-stage incentives for private capital to commit and compete to develop bioproducts. For example, the International Financing Facility for Immunisations (IFFIm, www.iffim.org) has been using this model for development and purchase of bioproducts since 2006.

   Advance Contingent Purchase Commitments can immediately be applied to Bioeconomy translational R&D as follows:
   - Government agencies define Target Product Profiles for high-priority products, and minimum purchase commitments for products achieving approval
   - Companies develop technologies through early stages to reach TRL-4 or higher
   - Once projects have met science milestones and achieved TRL-4 or higher, Government agencies make advanced contingent purchase commitments

- Government agencies authorize OTA-based commercial contracts to allow conversion of federal funds as pledges of debt service to support revenue bond financing and continuous, linked funding and financing of bioproduct R&D to science failure or product approval and availability

The Government can and should immediately establish and use Advance Contingent Purchase Authorities supported by taxable revenue bond financing in high-priority areas such as vaccines, medical countermeasures, defense and national security biomedical technologies, agri-bioproducts, biofuels, etc.

4. **Additional federal funding acceleration authorities** are available under Congressional authorities to the President, the Department of Defense, and other agencies to help protect the United States against diverse national security threats, including threats to public health from bioterrorism and pandemics. Special, fast-track government contracting and procurement processes, and contingent product purchase commitments, are authorized and have been used to attract private sector product developers to rapidly produce diverse defense and intelligence community priority products. These authorities, as well as advance commitments to next stage funding when major science milestones are met, can and should be used now to help address America's top public health threats.

5. **Financing Partnership Networks** are teams of private companies, Federal science and funding agencies, equity and debt investors, state and local economic development agencies, and strategic product end-users that can and will rapidly be drawn together and catalyzed by the recommended more efficient Federal funding into financing partnerships to push bio products to approval at the speed of science.

IMPACT

The Government can and should make a strong, immediate commitment to solving the grand challenge of improving the financing of translational science. This strategic solution will bring widespread positive impacts to America's Bioeconomy, e.g.:

- Empower Bioeconomy innovation to move at the pace of science, much faster than the pace of administrative procedure
- Accelerate Bioeconomy product delivery, job creation and economic growth
- Establish federal funding as a more effective component in delivering translational bioproducts and portfolios
- Establish strategic funding continuity and make Bioeconomy companies and projects investable
- Attract large new sources of private capital back into the funding of American innovation
- Ensure that American Bioeconomy innovation leadership leads to American Bioeconomy manufacturing leadership

The comments above are submitted by an informal group of scientists, entrepreneurs, executives, life sciences attorneys, contract research managers, venture fund managers, former senior federal officials and advisors, and public policy experts. These individuals have many years of combined experience and service in senior government, industry and academic roles in bioscience research and development and in attracting and managing private capital in the life sciences sector.

Respectfully submitted,
Dr. Charles Hamner
George Patterson
Leslie Platt
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December 6, 2011

MATHEMATICS: AN ENABLING TECHNOLOGY FOR THE 21st CENTURY BIOECONOMY

Society for Industrial and Applied Mathematics Response to Request for Information on the Bioeconomy Blueprint

In support of the Obama Administration's development of a Bioeconomy Blueprint, the Society for Industrial and Applied Mathematics (SIAM) offers below recommendations to promote problem-centric, interdisciplinary research to solve societal challenges in health, energy, environment, and agriculture.

Research is not only part of the bioeconomy, it is the very foundation from which the bioeconomy must build its success, and the Bioeconomy Blueprint should incorporate an aggressive and robust research portfolio to bolster expansion efforts.

As stated in the 2009 National Academy of Sciences report "A New Biology for the 21st Century: Ensuring the United States Leads the Coming Biology Revolution," new information technologies and sciences will be essential to creating a bioeconomy that can tackle societal challenges. The SIAM recommendations identify specific opportunities for the federal government to strengthen research and education at the interface between the life sciences and physical sciences, mathematics, and engineering.

SIAM is an international community with approximately 13,000 members from academia, industry, and government. Our members, from many different disciplines, have a common interest in applying mathematics in partnership with computational science towards solving real-world problems.

Grand Challenges (Q1)

Q1: Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, nonprofit organizations, foundations, and other stakeholders to achieve this goal.

As biology develops as a predictive science, new approaches to information analysis, data, and modeling will be needed to advance our understanding of the natural world in each societal challenge area.

Health: To make a transformational contribution to human health, an understanding of the genotype-phenotype problem, that is, the links between the genotype and phenotype of an organism is essential. Systemic diseases such as cancer are so challenging because they involve processes from the genome level to molecular networks inside a single cell, the tissue level and, finally, the entire organism, **all of which react to the external environment in a coherent fashion**. In fact, environmental influences are known to play a very important role in several disease processes. At the organ scale, recent advances in modeling the dynamics of blood flow in the heart and its connection to intracellular events

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provide unprecedented new tools for understanding heart disease and its effective treatment.

Energy: In order to expand sustainable alternatives to fossil fuels, new approaches beyond ethanol derived from corn must be developed. Microbial biocatalysis is a promising direction. In order to make it a reality, determining the link between genotype and phenotype will lead to the capability to engineer microbes from standard DNA modules that perform a specified metabolic function. Another promising approach is to engineer plants with molecular networks that produce more leaves and fruit without using additional fertilizer, thereby increasing energy production through photosynthesis. **With predictive models of the intertwined gene, protein, and metabolic networks, it becomes feasible to engineer and optimize organisms for efficient biofuel production**.

Environment: In order to sustain ecosystem functions in the face of rapid change, we need to be able to monitor multiple heterogeneous variables spanning a range of temporal and spatial scales. The **vast amount of data so collected needs to be integrated and used to construct unifying mathematical models that help guide environmental policy, and have the predictive capability to assess consequences of informed intervention**. Here too, the models need to integrate interconnected networks and systems of complex systems at vastly different scales, all affected by a common environment and subject.

Agriculture: In order to help ensure a sustainable and responsibly grown food supply, particularly in light of the changing global climate, one of the challenges is to understand and quantify how plants grow and interact with their environment. This involves characterizing the relationship between genotype and phenotype, a fundamental problem in biology. **At the genome level biology is essentially digital, and genetic sequence information is translated into dazzlingly complex interacting networks of genes, proteins, and metabolites, making up cellular function**. Cells organize into tissues, which, in turn form the whole plant. Functioning of the cellular networks is directly influenced by features of the environment the plant finds itself in, such as climate, resource availability, and microbial communities. Beyond the individual plant level, modeling will be necessary to be able to predict and control the ecology and spread of crop disease, invasive species, and other agricultural threats.

The importance of developing better modeling, computational, statistical, and analytical tools to enable a better understanding of biological systems and detailed discussion of the potential impact and key problems are also described in the 2005 National Research Council report "Mathematics and 21st Century Biology."

COMMON THEMES

Three common themes emerge from the challenges named in the RFI.

1. **All four challenges require the construction and analysis of predictive mathematical models of large, nonlinear dynamic networks that span several spatial and temporal scales.** Understanding and manipulating these systems will require large, multi-scale, nonlinear, and hybrid models. Existing simulation and analysis tools for such models are in their infancy, or nonexistent in some cases. For

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instance, an increasingly popular modeling paradigm for complex networks in fields ranging from molecular biology to ecology is agent-based modeling, which captures the important feature of many complex systems that global behavior emerges from local interactions. Very few analysis tools exist for such models. For many applications it is desirable to use models to predict how interventions on one level will impact biological systems on other levels, such as in the development of therapeutics. This process requires control approaches, but for the systems at the heart of the New Biology challenge areas, it is sometimes difficult or impossible to apply existing control theoretic approaches.

2. In all problem areas **high performance computation will play a crucial role, from simulating complex multi-scale models to analyzing sequence data**, e.g., multiple sequence alignment. **This will require new breakthroughs in algorithm development**, since we cannot expect significant increases in clock speed due to silicon technology. Performance improvements in computation will come from more cores on a chip. This means significant changes in algorithms to take advantage of parallelism on the chip as well as parallelism between computational nodes comprised of multiple chips. In order to achieve high rates of performance, algorithms that minimize data movement, possibly at the expense of doing additional computations, will be the most efficient. Algorithm developers will need to take these facts into account as they develop multi-scale, multi-physics algorithms.

3. In all four challenge areas we face **ever-growing data volumes**, from DNA sequence data to satellite surveillance data. These data need to be stored in databases that are easily accessible and searchable, requiring increasingly sophisticated and scalable data mining algorithms. In addition, the data from heterogeneous sources need to be integrated, within databases as well as within models. Once accessible in databases, the typically high dimensional data sets need to be analyzed using statistical methods. In order to meet these challenges, new tools from multivariate statistics and discrete mathematics are needed, in particular graph theory and combinatorics.

Research and Development (Q2-3)

Q2: Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

The three themes, described above, that are common to all four challenge areas make clear that mathematics is indeed an important enabling technology for the bioeconomy. **We recommend that any funding programs related to the Bioeconomy Blueprint provide support for mathematical research related to the problems identified above in the following areas:**

1. Complex networks, both in the graph-theoretic sense and in the dynamical systems sense.
2. Multi-scale modeling and simulation, including computational science research to enable new approaches.
3. Nonlinear partial differential equations.
4. Algorithms for high performance computation.
5. Algorithms for new multi-core computer architectures.

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6. Multivariate statistics.
7. Dynamical systems.
8. Hybrid models.
9. Control theory.
10. Combinatorics and graph theory.
11. Data mining algorithms.
12. New methodologies for modeling complex stochastic biological systems.
13. Quantification of model uncertainty.
14. Numerical analysis.

In addition to research in these areas, it is becoming increasingly clear that there is much untapped potential in mathematical fields that are not traditionally considered as applied. Good examples are recent applications of algebraic geometry to biological problems and the use of methods from algebraic topology for high dimensional data analysis. (Within SIAM, recognition of these emerging opportunities has led to the establishment of a new SIAM Activity Group in Algebraic Geometry.)

RESEARCH SUPPORT MECHANISMS

To support the research areas outlined above, programs at individual agencies and interagency initiatives will be needed. Specifically, **an array of complementary approaches will be needed – from those that focus on building expertise in a single topic area, often at a single agency, to application-driven programs that combine mission agency's user communities and discipline-organized research programs.** Agencies likely to have relevant expertise, communities, programs, and missions include: the National Science Foundation (NSF), the National Institutes of Health (NIH), the Department of Energy (DOE), the U.S. Department of Agriculture (USDA), the Department of Defense (DOD), the Environmental Protection Agency (EPA), the Department of Homeland Security (DHS), and others.

There are a number of existing programs that effectively support research at the interface of mathematics and the life sciences. These programs could be expanded or used as models for the establishment of new programs. Examples of existing programs include:

- NSF-NIH collaborations, such as the long-standing NSF Division of Mathematical Sciences (DMS) program with the NIH National Institute of General Medical Sciences on applications of mathematics to biomedicine and the new NIH-NSF programs at the Interface of the Life and Physical Sciences.
- NSF-DOD collaborations, such as the recently-established NSF DMS program together with the Defense Threat Reduction Agency to develop the next generation of mathematical and statistical algorithms and methodologies in sensor systems for the detection of chemical and biological materials, and the NSF program under development with the U.S. Army to develop mathematical algorithms to integrate and analyze heterogeneous battlefield sensor data.

Mechanisms should be available to support a variety of sizes of research projects, from individual investigators to center-scale collaborations. Examples of multi-agency and single-agency center-scale initiatives in this area include:

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- The National Institute for Mathematical and Biological Synthesis (NIMBioS), jointly supported by the NSF Biological Sciences Directorate and DMS, together with USDA and DHS.
- NSF DMS also supports the Mathematical Biosciences Institute (MBI) at the Ohio State University.

Both institutes focus on research at the interface between mathematics and biology and foster interactions between mathematical scientists and bioscientists.

Q3: What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

To realize the potential of high-throughput molecular approaches, **new computational algorithms as well as new theoretical mathematical and statistical approaches are needed to extract patterns from large volumes of high-dimensional data.** It used to be the case in molecular biology that the expense and difficulty of data generation far outstripped the expense of data analysis. This situation is now reversed. Data analysis now typically consumes as much as 75 percent of project resources. New data generation technologies, such as next generation sequencing, tilt this balance even further in the direction of data analysis. The quantity and complexity of new high throughput data types poses serious challenges to the extraction of information and, ultimately, knowledge from molecular data.

While new data analysis approaches are critical to overcoming the high throughput data deluge, it is also important that centers producing data are equipped and willing to shift to these new approaches. Too often genomics centers lack the knowledge of how to use new techniques and the willingness to integrate or replace current practices. Federal programs should encourage the transfer of research on data analysis to genomics and other high throughput centers.

Workforce development (Q9)

Q9: The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Training for mathematicians, scientists, and engineers should explicitly foster skills needed for the bioeconomy workforce. These skills include the ability to work in diverse teams that straddle expertise areas and disciplines, innovative thinking oriented around solving real-world problems, and communication with non-scientists. Federal training programs should encourage university efforts to foster these skills. The NSF Integrative Graduate Education and Research Traineeship Program is an example of a federal graduate training program that encourages mentorship, career development, hands-on experience with innovation and translating research discoveries to solutions for societal challenges. These **best practices should be expanded beyond the frontier interdisciplinary programs that IGERT supports to graduate training across all fields relevant for the bioeconomy.**

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As one example of a skill needed for the bioeconomy workforce, mathematical scientists and statisticians in both academia and industry will need appropriate awareness of the interdisciplinary research questions central to the bioeconomy challenge areas. Programs should be implemented to ensure this pipeline of mathematicians and statisticians at the undergraduate, graduate, post-doctoral, and early career levels. It will also be critical to train biological scientists with highly developed quantitative skills and interdisciplinary experience.

For example, **mathematicians would benefit from a new program that supports university efforts to develop curricula and programs focused on horizontal integration of mathematics training with other disciplines.**

In addition to programs that support research activities, federal agencies should focus on raising awareness in the biological and mathematical communities about science at the interface and facilitating cross-disciplinary collaborations, as creating research teams and partnerships across disciplines takes more time and conversation than building teams of people who are within a discipline and share a common culture. In addition, outreach within each community about interesting results in one discipline that may potentially be relevant to problems in the other discipline could have a significant impact (i.e. the discovery of applications of algebraic geometry to biological problems mentioned above). Such unexpected linkages can bring very high returns, and their development should be systematically fostered and supported.

To accomplish the above goals, programs that support network creation, workshops, travel, and summer programs, would be useful. "Sabbatical" cross-disciplinary opportunities for researchers, post-doctoral students, and graduate students would help create a new community of researchers more alert to and equipped to conduct interdisciplinary research. The new NSF Science, Engineering, and Education for Sustainability Fellows is an example program that supports this type of activity.

In order to train students for jobs outside of academia, Federal agencies should also encourage increased collaboration between industry and universities. **Fellowships that allow students to spend part of their graduate careers working in industry or other sectors help create networks between academia and industry, foster real-world learning, and provide students with greater understanding of workforce opportunities beyond the lab. Collaborative research with industry and orienting research towards grand challenges defined in concert with industry help foster student awareness of industry challenges and skills.** The NSF Grant Opportunities for Academic Liaison with Industry (GOALI) program is an example of Federal funding that catalyzes industry student exchanges and research collaborations.

Conclusion

SIAM thanks you for your consideration of these recommendations. We look forward to working with the Administration to help define and implement the mathematics and information sciences programs needed to take full advantage of research at the mathematics/biological sciences interface and move us toward solving societal challenges such as those outlined in the Bioeconomy Blueprint RFI.

Building a 21st Century Bioeconomy

Comments by the Advanced Medical Technology Association (AdvaMed)

Overview

AdvaMed is the world's largest medical technology trade association, and represents manufacturers of medical devices and diagnostics. AdvaMed members account for approximately 90 percent of these products consumed in the United States and 50% of those consumed worldwide. The companies in our industry produce virtually everything used in medicine that is not a drug—from products as simple as tongue depressors and surgical gloves to the most complex cardiac implants, imaging machines, and molecular diagnostics.

AdvaMed is enthusiastic about the President's vision for a national bioeconomy blueprint. We believe that our industry, along with other life sciences industries, can be a key driver of future economic growth and job creation. But achieving that potential will depend on a new commitment to comprehensive public policies to maintain America's leadership in this century of the life sciences.

Economic potential of medical technology

The medical technology industry is not only a source of life-enhancing and life-sustaining treatments and cures; it is an important manufacturing industry and a driver of current and future U.S. economic growth. The industry employs more than 420,000 people in the U.S. It generates an additional four jobs in suppliers, component manufacturers, and other companies providing services to the industry and its employees, for every direct job—for a total of more than two million jobs nationwide.[1] Medical technology jobs are good jobs, with wages exceeding those for the work force as a whole by 40 percent and exceeding average wages in other manufacturing industries by 22 percent.[2]

While employment in other manufacturing industries has been declining, the medical technology industry has been expanding. Between 2005 and 2007, medical technology employment grew 20.4%, adding 73,000 jobs.[3] During the recession, between 2007 and 2008, MedTech employment dropped 1.1%, compared to 4.4% for manufacturing as a whole.[4]

The medical technology industry is also a strong source of exports and is almost alone among manufacturing industries in consistently maintaining a favorable balance of trade. Exports in 2010 totaled $36 billion, more than double the 1998 level.[5]

Part of the vitality of the medical technology industry comes from its strong base of small and start-up companies, which develop a disproportionate number of the breakthrough products fueling industry growth. A 2007 study by the U.S. International Trade Commission (USITC)

found a total of 7,000 medical technology firms in the U.S.[6] The U.S. Department of Commerce estimated that 62% of medical technology firms had fewer than 20 employees and only 2% had more than 500.[7] Even large companies in the medical technology space tend to be smaller than large companies in many other sectors. There are only four pure device and diagnostic companies in the Fortune 500 and none in the Fortune 100.

Another source of industry strength is its strong commitment to research. To fuel innovation, the medical device industry is highly research intensive. U.S. medical technology firms spend over twice the U.S. average on R&D. High technology medical device companies devote upwards of 20% of revenue to R&D.[8]

The medical technology industry is highly price-competitive. A study of medical device prices from 1989 to 2009 found that they increased, on average, only one-quarter as fast as the MCPI and one-half as fast as the regular CPI. Because the highly competitive market kept prices low, medical devices and diagnostics accounted for a relatively constant 6% of national health expenditures throughout the 20-year period despite a flood of new products that profoundly changed medical practice.[9]

The future potential for American economic growth driven by the medical technology is great. World-wide markets for medical technology will expand dramatically as populations age in countries around the globe In the U.S. alone, the elderly population will increase 32 million over the next two decades—a jump of 80%.[10] Worldwide, the elderly population will reach 1.2 billion by 2025—and growth of the elderly in that year will be 3.5 times as fast as the population as a whole.[11]

World-wide demand for medical technology will also be fueled by the exponential growth in middle-class populations in countries like China, India and Brazil demanding world class medical care. China's middle class alone is projected to exceed the entire U.S. population by 2015, and India's middle class could reach 600 million by 2025.

Growth in medical technology will also be fueled by scientific progress in this century of the life sciences, as fundamental discoveries in the life sciences and continued advances in computing, materials, engineering, and physics create the knowledge base for an explosive growth in the creation of new treatments and cures. To quote Dr. Laurence Summers, president emeritus of Harvard University and former head of the National Economic Council, *"*The 20th century was an American century in no small part because of American leadership in the application of the physical sciences...If the 20th century was defined by developments in the physical sciences, the 21st century will be defined by developments in the life sciences*."*

Medical technology and the other life sciences industries also have the potential to fuel economic growth by their role in creating a healthier work force. As a major driver of medical progress and improvements in population health, medical technology is an engine driving productivity and labor force participation, both significant contributors to economic growth and GDP.

Between 1980 and 2000, medical progress added more than three years to life expectancy. The death rate from heart disease was cut in half, the death rate from stroke was cut by one-third, and the death rate from breast cancer was cut 20%.[12] The economic value of the reduction in death and disability from heart disease alone has been equal to one-fifth of our total GDP.[13]

The Milken Institute has compared two alternative futures regarding the growth in chronic disease. Under one path, the current trends in growth in the incidence of chronic disease continue unchecked. Under the other path, the growth is reduced significantly by a combination of better prevention, better management, and continued technological progress in treatment. The difference between the current trend path and the more favorable path was estimated to be $1.1 trillion in GDP annually by 2023, primarily because of the increased labor force participation and productivity as the result of better health.[14] Similarly, the United BioSource Corporation examined the literature on the economic burden of lost productivity due to eleven chronic and two acute conditions. They concluded that the total drain on the nation's GDP in 2008 from lost productivity and labor force participation due to these conditions was as much as $1.4 trillion annually in 2008.[15]

Need for better policy to sustain American leadership

Today, America is the acknowledged world leader in medical technology, as it is in the other life sciences industries. But that leadership is being challenged. Without new public policies to provide a level playing field between the U.S. and foreign competitors, America's leadership will be lost and with it an important engine of economic growth and manufacturing job creation. At a more profound level, if American leadership in the life sciences industries is lost, America's long-term future as the world's most powerful economy will be jeopardized. Thus, the President's efforts to develop the National Bioeconomy Blueprint are particularly timely.

A recent study by PricewaterhouseCoopers (PwC) found that the U.S. still leads on five key dimensions of medical technology innovation, but our lead is slipping on every dimension. On speed of regulatory approval, we now rank seventh out of nine countries. As they state, "The innovation ecosystem for medical device technology, long centered in the United States, is moving offshore."[16] Indeed, a recent survey of AdvaMed member companies found that while companies projected employment growth over the next five years both in the U.S. and abroad, employment growth was projected to be more rapid abroad—in both percentage and absolute terms.

The slippage of American leadership shows itself in a number of ways. Medical device and diagnostic clinical trials—a crucial step in the development chain—are increasingly conducted outside the United States. In 2004, 86.9% of all medical technology clinical trials listed in ClinicalTrials.gov were carried out in the U.S. By 2009, that proportion had sunk to 45%. The cumulative annual growth rate of U.S. clinical trials 2004-2009 was lower than that of Brazil, China, France, Germany, India, the U.K., Israel, and Japan.[17]

First product introduction is also increasingly moving outside the United States, as firms find that they can get products approved much more quickly abroad. The average lag time between introduction of a complex product in Europe and introduction of the same product in the U.S. is now almost four years.[18] Key products that have become available in Europe while languishing in the U.S. approval system include important clinical advances in such areas as heart disease, lung disease, obesity, and arthritis.[19]

The movement of clinical trials and first product introductions abroad is not only harmful for American patients, who find their access to the latest treatment and cures significantly delayed; it is also a drag on U.S. competitiveness. In addition to the economic activity generated by the clinical trials themselves, location of trials and early product introduction transfers expertise out of the U.S.

The recent sharp decline in FDA performance is striking and very damaging to industry competitiveness. Since 2007, the average review times for 510(k) products has increased 45 percent. The average time to review PMA products—the most complex and typically the most innovative technologies—has skyrocketed 75 percent.[20] Measures of consistency in review—such as the average number of times the FDA sends an application back to a company to ask for additional questions, the number of times reviewers change during the course of a review, and the proportion of times companies withdraw applications before reviews are even completed—have also increased substantially.[21] It has become more difficult to get a timely and meaningful meeting with the FDA to discuss clinical trial design, and the time it takes to get approval to begin a clinical trial has grown substantially.[22]

These failures at the FDA are a key factor driving clinical trials and first product introductions abroad. They add to the costs of American companies and undermine investments in new products. Small companies with promising ideas frequently do not survive because they run out of funds before they can get FDA approval and generate revenue. Improvements at FDA are one of the most important steps that can be taken to sustain American competitiveness and leadership. Fortunately, the current FDA leadership has acknowledged the seriousness of these problems and is making efforts to reverse these trends.

America's commanding lead in venture capital investment in medical technology is also eroding. As noted above, small, venture capital funded firms have been a key factor in creating the breakthrough products that drive industry growth. Comparing 2000 and 2009, venture capital investment in medical technology grew almost 60% in Europe and Israel and less than 40% in the U.S.[23] Overall, the availability of venture capital in other countries is growing dramatically. China now represents the second-largest pool of venture capital, followed by Brazil.[24]

Not only is venture capital growth in the U.S. slower than abroad, growing regulatory and payment uncertainties in the U.S. are causing VC firms to rethink whether they want to invest in

the medical technology sector. Moreover, as they see longer time—and thus greater cost—in getting products to market as the result of these uncertainties, they are planning to invest the same amount of dollars in fewer companies and shifting investments more to companies that are further along in the development process.[25] This exacerbates what is often referred to as the "valley of death" problem, where promising clinical discoveries can receive support for very early stage research, but funding often dries up before the product can reach the stage where it is ready for regulatory review.

The U.S. reimbursement system has historically been relatively open to new technologies, and this has been a significant strength for the U.S. medical technology industry. The role of government programs is especially important. In 2008, Medicare and Medicaid together paid for medical care that accounted for an estimated 48% of total domestic sales of medical technology products.[26] Medicare policies are especially critical, because not only do program beneficiaries use a large proportion of medical technologies, Medicare payment and coverage policies are often the model for decisions by private insurers.

While the U.S. system overall has enabled rapid adoption of new technologies, current policies should be improved. For example, gaining a code for a new product—which is often a prerequisite for Medicare or private insurer payment—can take up to two years or more after a product gains FDA approval.[27]

An additional important problem affecting medical technology innovation is the antiquated and inconsistent system Medicare uses for deciding what to pay for new laboratory tests under the Clinical Lab Fee Schedule. The new generation of molecular diagnostic tests is, in many respects, key to the future of medicine. They are the basis of the emerging field of personalized medicine. They can provide extraordinary precision and speed in diagnosis. They can be used for drug development and drug targeting. But the Medicare payment system does not recognize the value of diagnostic tests, and the payment any new test will be assigned is arbitrary and unpredictable. Such uncertainty creates a significant disincentive for companies to make the sizable investments necessary to develop these new tests.[28]

Major changes in U.S payment methods currently in progress pose a significant challenge to medical progress and need to be carefully implemented to avoid exerting a chilling effect on medical technology. The new payment modalities being created for Medicare by the health reform bill as well as payment innovations in the private sector are designed to encourage efficiency, quality, better coordination of care, and better management of chronic diseases. While these new payment paradigms offer the promise of a more efficient and effective health care system, the new systems also create some potential pitfalls that could negatively affect innovation and medical progress if the new systems are not carefully designed to encourage innovation.

The widespread adoption of an improved treatment or cure generally follows a typical path. The treatment is developed by a company or a physician. Following FDA approval (in the case of a drug or device) the new treatment is adopted by cutting-edge physicians and is recognized by insurance companies and other payers. If the treatment proves successful in practice, it gradually diffuses until it becomes the standard of care.

Without special protections for innovation, the new changes in health care delivery models and the application of quality standards to reimbursement risks freezing medical practice in place. New delivery models must ensure patient access to appropriate devices, diagnostics, and other medical technologies and must not penalize early adopters of new technology. The current quality standards are generally "process" standards—for example, for a given specific disease state, a certain course of action should be followed.[29] For example, patients presenting with a heart attack are supposed to be treated with percutaneous coronary intervention (PCI) within 90 minutes.[30] The new payment modalities embed these quality standards in the level of payment physicians and other providers will receive. Without special provisions in the reporting and payment system, providers who are early adopters of a new, alternative treatment—a new drug or procedure to replace PCI—will be penalized.

The same concern applies to adoption of new treatments that appear to be more expensive than the existing standard of care. Not only does the early adopter face a potential penalty on the quality side, but they also could be treated as inefficient because they are generating higher costs—even if the new treatment represents a significant clinical advance.

Providers could be penalized even if the new treatment actually lowers costs, if the savings appear outside the measurement window. For example, under bundled payments—where all providers treating a patient during an episode of care receive a single, lump sum payment—costs are measured across the episode of care. A drug-eluting stent that reduces costs over the long-term by reducing the need for repeat procedures would appear more expensive than a bare metal stent. So would a heart valve or a knee replacement that lasts for 20 years instead of ten years or other treatments that have better outcomes over a more extended period than the immediate episode of care.[31]

The final rule for Accountable Care Organizations, the first of the new payment modalities to be fully implemented has just been released. Despite the President's recent Executive Order directing agencies to "seek to identify, as appropriate, means to achieve regulatory goals that are designed to promote innovation," the proposed rule does not address these issues.

Trade policies of other countries—particularly in the developing world—are increasingly designed to foster home-grown medical technology industries at the expense of U.S.-based companies or to require U.S. companies to locate research and development or production facilities locally as the price of market access. For example, China has developed an "Indigenous Innovation" policy in its government procurement—which could well include the vast public

hospital sector—that is intended to require purchases of products with "domestic" intellectual property and to force the transfer of technology to domestic companies.[32] Brazil's has a stated policy to expand its use of domestic medical technology, including by providing 25% price preferences for government procurement (about half of its heath care expenditures) and to use its product approval regulatory agency to favor domestic medical technology firms.[33] In addition, other countries are pursuing bilateral and regional trade agreements that will put U.S. manufacturers at a competitive disadvantage.[34]

Competitor countries are also aggressively implementing tax and other policies that effectively lower the cost of research, development, and manufacturing of high technology, high value products such as medical technology. America's failure to match these incentives creates an unlevel playing field for products developed and manufactured in the United States. The U.S. has one of the highest effective corporate tax rates in the world. For a typical small or medium sized business, the effective tax rate in the U.S. is 25.9%, higher than 31 out of 34 Organization for Economic Cooperation and Development countries and 58% higher than the non-U.S. OECD average of 16.4%.[35] The U.S. was the first country to establish an R&D tax credit, but 23 countries now offer a more generous credit than we do. Our reliance on temporary extensions of the credit means that it does little to stimulate investment, since it cannot be relied on for planning purposes. The credit does not cover building R&D facilities or purchase of equipment for those facilities, even though the decision to locate an R&D facility in a particular country certainly stimulates further R&D investment to make use of the facility.

Small, start-up companies have no access to the R&D tax credit until they actually have profits. This imbalance exacerbates the cash flow issues that often kill promising ideas and promising companies before they can attain critical mass and defeats the purpose of the credit—to stimulate research and development.

Other countries are experimenting with so-called "innovation box" or similar ideas that provide a reduced corporate income tax for profits flowing out of manufacturing or other activities based on research and development. It makes no sense for American scientists and engineers to develop breakthrough treatments here in the U.S.—and then ship the good manufacturing jobs needed to make those products abroad, because taxes here are so much higher.

An additional tax policy that harms American competitiveness is that the U.S. is one of the few countries among our competitors that maintain a territorial tax system. Other countries do not tax the profits that their companies earn abroad. In the U.S., however domestic taxes are only deferred until U.S. companies bring the profits home. The result: U.S. multinationals are penalized if they invest profits earned abroad in America instead of using them to build research and manufacturing facilities overseas.

In addition to general tax incentives, other countries provide targeted incentives for projects that offer jobs and economic growth, especially projects in high value-added industries. These

incentives include waiving or reducing taxes on the project, providing direct subsidies in the form of below interest loans or grants, or making land and infrastructure available as needed.

Developing countries have been particularly aggressive in working out special deals to attract job-creating projects. India, for example, is building a series of industrial parks expressly designed to attract medical technology investment and the jobs that foreign companies will bring.

The net effect of these strategic policies by other countries, combined with lack of effective American policies to level the playing field, have had the effect of dramatically shrinking America's favorable balance of trade for medical technology products. While the U.S. has maintained a favorable balance of trade, the surplus of exports over imports has been narrowing both in absolute terms and relative to the size of the export-import sector. In 1998, imports and exports together totaled $24.6 billion and the trade surplus was $6.6 billion—more than one-quarter of total trade. By 2010, total trade had almost tripled—to $70 billion, but the trade surplus had shrunk by more than two-thirds—to $2 billion, and the surplus was only 3% of total trade. [36]

While America's commercial advantages have been slowly eroding, the fundamental superiority of America's scientific research and development infrastructure and its ability to turn research into commercial projects is increasingly challenged. America's science base, including basic research, the supply of scientists and engineers, and vitality of America's universities as centers of basic and applied research, is critical to the medical device industry, as it is to America's leadership in science and technology more generally. A number of studies have documented the relative decline of America's science base by such measures as R&D investment as a share of GDP, new patents as a share of the global total, global share of scientific researchers, and new doctorates in science and engineering.[37]

Policy Recommendations

Despite these negative trends, American leadership can be retained and strengthened. A renewed government commitment to strategic policies to maintain medical technology competitiveness by leveling the playing field with foreign companies and governments is needed. The President's National Bioeconomy Blueprint is an unprecedented opportunity to help build America's future prosperity.

AdvaMed has advanced six key policy recommendations to assure America's continued leadership in medical technology. They are:

1. **Innovation in the life sciences must be a government priority**. Since the ability of the life science industries to thrive is affected by a broad range of government policies across many agencies, it is critical that that supporting medical innovation be a priority for the whole government.

A. An office of medical innovation policy should be created in the White House. This office would have oversight responsibility for major proposed and current government policies to assure that they support medical innovation. The office would serve as a focal point for groups and individuals advocating for medical innovation and could develop an innovation index to track how well the United States measures up to its major competitors in policies to encourage innovation.
B. An "innovation impact" statement would be required for major regulations or other actions that affect the health sector. This statement would be analogous to an environmental impact statement. The goal would be to assure that every agency takes into account the effect of its actions on medical innovation and related domestic employment, and economic growth in promulgating government rules.

2. **The FDA review process must be reformed**. The FDA must set a goal of achieving a review and approval process that is as predictable, consistent, and timely as our European competitors, while continuing to assure that products are safe and effective.

A. FDA must reduce total review times, not just time on the FDA clock, to a level that will significantly speed up review of both 510(k) and PMA products, including reforming the de novo process to make it an efficient and workable system for class II products with no predicate.
B. FDA must effectively implement least burdensome processes throughout its operations to eliminate requirements that are not necessary to protect public health.
C. FDA must streamline the IDE process to assure timely initiation of clinical trials.
D. FDA must develop a full range of guidance documents that identify FDA's requirements for a specific product submission to ensure a timely and consistent review process.
E. FDA must adopt the risk-based review pathway for diagnostic tests.
F. The FDA must take steps to ensure that its staff is properly trained, has access to independent scientific and technological information, and to develop a program to monitor the predictability and consistency of the review process.
G. FDA must take steps to converge its regulatory practices with the principles established by the Global Harmonization Task Force.

3. **Payment policy must support medical innovation**. Medicare, Medicaid, and private insurers alike must assure that the new payment modalities established by health reform to provide incentives for quality and cost control also support medical progress, innovation and access to appropriate technology. The current Medicare coding and payment processes must be improved to allow more rapid recognition of new technologies.

A. New payments systems such as accountable care organizations, bundling, and value-based purchasing should include specific provisions to avoid penalizing

health care organizations or individual providers for offering patients the opportunity to benefit from new treatments that are not yet the standard of care.

B. New payment systems should be carefully designed to support continued patient access to care appropriate for their individual needs and to recognize the long-term value of treatments.
C. CMS should reform the process of coding and determining appropriate payment to avoid delays of up to two years or more before a treatment can be properly recognized for payment purposes.
D. CMS should reform payment for new diagnostic tests to encourage the development of high value diagnostics and of personalized medicine.

4. **A vigorous trade policy must support export growth and provide a level playing field for U.S.-based manufacturing**. If trade barriers remain or increase, U.S. efforts to improve domestic competitiveness and expand exports would be undermined. Companies will relocate outside the U.S. to manufacture behind the barriers and foreign companies will thrive at the expense of U.S. competitors. Other countries are pursuing bilateral and regional trade agreements that will put U.S. manufacturers at a competitive disadvantage. Countries in the developing world are increasingly using regulatory policy to promote domestic industries or to force U.S. companies to locate research, development, and manufacturing within their borders. Small and medium size companies need additional assistance to become successful exporters.

A. The President's National Export Initiative (NEI) should make bilateral and regional free trade agreements (and associated medical technology sectoral agreements) with developed and developing markets alike a priority, including ratification of the Korean-US free trade agreement, negotiation of the TransPacific Partnership free trade agreement and expanding the agreement to include additional Asia-Pacific countries, including Japan.
B. The Administration should continue its policy of vigorous opposition to non-tariff barriers to trade, especially use of regulatory policy to set up artificial barriers to imported products and to force local location of research and development and manufacturing by multinational firms. The Administration should support existing and new trade forums that allow government officials and industry representatives to work together to identify and address barriers to trade. FDA should be part of the team working with trade authorities and indicate that assistance to foreign firms seeking to meet U.S. regulatory requirements is conditional on fair treatment of U.S. firms by foreign regulatory authorities.
C. The Administration should make regulatory harmonization by developing countries a trade priority, including achieving a commitment next year to regulatory harmonization by 2020 at the Leaders meeting of the Asia Pacific Economic Cooperation forum, based on the principles adopted by the Global Harmonization Task Force.
D. Small and medium size enterprises represent the lifeblood of medical technology innovation. Exporting to foreign markets is particularly difficult for companies with little or no foreign trade experience. Under the NEI, US Government agencies – including USTR, SBA, and Commerce – should vigorously pursue

policies to assist small and medium size companies to overcome their lack of experience and specialized knowledge, and other obstacles to competing in export markets.

5. **Strategic tax policies to level the playing field must be implemented.** *American tax policy must support research and development (R&D)* intensive industries at a level sufficient to level the playing field with foreign governments eager to attract American jobs and develop home-grown competitors to American firms. The R&D tax credit must be reformed and made more generous; tax incentives need to created for keeping R&D based manufacturing in America. The medical device excise tax should be repealed.

A. The Research and Development Tax Credit needs to be made permanent; the level of the credit needs to be raised so that it is as good or better than the credits provided by our major competitors; the administration of the credit should be substantially simplified; the credit should support investment in building research infrastructure, including construction of facilities and purchase of equipment; and the tax code should provide additional incentives to invest in small and start-up companies with no profits, which create a disproportionate share of breakthrough treatments.
B. Manufacturing based on R&D wholly or predominantly conducted in the United States should be eligible for a lower corporate tax rate to reduce the cost advantage that research and development intensive companies locating manufacturing abroad enjoy in the form of lower general corporate taxes, special tax breaks, and direct subsidies.
C. The medical device excise tax should be repealed, since it absorbs resources that could otherwise be used for research and development or employment expansion and disproportionately burdens and raises the effective corporate tax rate for the medical technology industry to extremely anticompetitive levels.
D. The United States should move towards a corporate tax system that provides greater parity with our major competitors in tax rates and treatment of foreign earnings.

6. **The American research and development infrastructure must be sustained and improved.** American policy must support the maintenance and growth of an R&D infrastructure second to none, with special emphasis on creating the structures necessary to support translational R&D directed at commercialization.

A. America must maintain and expand its commitment to basic research and to graduate research and training programs through the NIH and NSF.
B. Research programs that support moving research farther along the development spectrum toward actual treatments and that support start-up companies developing

breakthrough treatments should be improved and expanded, including increasing funding, eligibility, and maximum grant size for the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR programs) and fully funding the Cures Acceleration Network. Additionally, the federal government should provide grant funding to states and localities seeking to establish or expand bioscience research and development clusters.

C. Programs should be established to more effectively tap the vast intellectual resources of our nation's universities and academic health centers, including creating NIH funded Industry-University Cooperative Research Centers analogous to a long-standing and successful program at the NSF and providing federal technical assistance to establish best practices and improve the effectiveness of university technology transfer programs.

The detailed rationale for these proposals is described in "Backgrounder: The American Medical Technology Industry and American Competitiveness, " which can be found on the AdvaMed web site at: http://www.advamed.org/NR/rdonlyres/F015B6D3-B805-4405-8F44-646D49265830/0/CAgenda_Backgrounder.pdf

In addition, some of these proposals are discussed further in answers to specific questions posed by OSTP in its Request for Information.

Responses to Specific Questions in the "Request for Information: Building a 21st Century Bioeconomy."

1. Grand challenges

As described at some length above, the grand challenge the U.S. faces in building a 21st Century Bioeconomy is to create and sustain an innovation ecosystem for the life science industries and to create a level playing field with competitor nations. Each of the six steps described above would contribute to that goal.

2. Constrained Federal Budgets

A number of Federal priorities are critical within a constrained Federal budget. These include:

--Maintain funding for the FDA. An inadequately resourced and managed FDA would be a disastrous choke point for all the life-sciences industries. The U.S. can lead in the life sciences only if the FDA supports innovation through a consistent and timely regulatory review process.

--Assure that pressures for cost containment do not lead to a hostile climate for medical innovation in the federally supported health programs. With regard to the specific issues related to the new payment modalities, suggestions are provided above. Other concerns are excessive cuts in provider reimbursement or inappropriate limitations on coverage of or payment for new technology in the name of cost control.

5. Barriers preventing biological research discoveries from moving to the lab to the commercial markets

It is important to recognize that moving discoveries from the lab to commercialization is a resource-intensive, high-risk business. Several steps would be helpful:

-- Research programs that support moving research farther along the development spectrum toward actual treatments and that support start-up companies developing breakthrough treatments should be improved and expanded, including increasing funding, eligibility, and maximum grant size for the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR programs) and fully funding the Cures Acceleration Network.

--The flow of venture capital and other funding to start-up firms needs to be increased. A variety of tax preferences to encourage investment in these firms should be considered.

--University technology transfer programs vary widely in their effective. Many, if not most, are viewed by device and diagnostic companies as difficult to work with. The Federal government should take the lead in helping technology transfer programs adopt best practices.

--The most important single step that could be taken right now for the device industry, as discussed above, is to improve the predictability and efficiency of FDA review.

6. Specific Changes to the SBIR and SSTR programs

Current limitations that bar start-up firms with majority venture capital funding from eligibility for grants are too limiting, given the need for start-up companies to receive significant amounts of venture capital funding to bring products to market. These limitations should be eliminated.

In addition, in view of the rising costs of product development, the limits on the amount of SBIR grants should be raised and overall funding for the program should be expanded.

8. Challenges associated with existing private-sector models for financing

See the data described above on the drying up of venture capital funding for investment in medical device and diagnostic companies, especially for early-stage start-ups.

A variety of tax changes should be considered to encourage venture and angel investment in these companies.

The most important change to restart the flow of capital into early stage companies, as noted above, is improvements to the efficiency and predictability of FDA review.

13. What specific regulations are unnecessarily slowing or preventing bioinnovation.

AdvaMed submitted a letter (attached) to the Secretary of HHS listing some regulations or subregulatory guidances that should be dropped or modified regarding FDA regulation of devices.

With regard to payment regulations, the impact of the new payment modalities included in health reform is still hypothetical. However, the potential for unintended consequences that would have a chilling effect on innovation is significant and can be avoided without undercutting the goal of the new modalities to improve efficiency and quality. The problem is described above. AdvaMed's specific recommendations were described in detail in its comments on the ACO proposed rule.

In brief, AdvaMed recommends that:

--Benchmark spending targets and shared savings pools under ACOS, bundling or other new payment modalities should keep pace with advances in medical treatments and technologies by including adjustments for a reasonable period of time during which a new innovation is diffused and becomes the new standard of care. CMS would determine which advances would qualify. Adjustments would be modeled after those used in the Medicare program today for inpatient and outpatient hospital care but would be broader in application.
--Similarly, quality care measures should keep pace with advances in medical treatments and technologies. In calculating bonuses or penalties, certain cases should be excluded for a reasonable period of time when existing quality measures do not reflect the new treatments available to patients.

In addition, quality under the new modalities needs to be carefully monitored to assure that incentives to reduce costs do not lead to patients not being offered the most appropriate treatment for their condition.

As noted in recommendation #3d in the AdvaMed innovation agenda above, it is critical that the antiquated Medicare payment system for clinical laboratory tests be modernized to reflect the value of new molecular diagnostic and other innovative, high impact laboratory tests.

At a more general level, the whole regulatory process of government needs to be more attuned to the need to foster innovation and competitiveness in the life sciences—particularly for agencies, such as CMS, that do not see innovation as part of their mission but nonetheless have a major impact on the life science industries. Accordingly, as noted in item #1 of the innovation agenda, all agencies issuing major regulations or taking major subregulatory actions that have the potential to impact health care or health research should be required to include an "innovation impact" statement, analogous to the environmental impact statement currently required of many rules. In addition, an office of medical innovation should be created within the White House that could provide oversight of disparate government agencies to assure that their actions support medical innovation and offer a focal point for discussion with groups and individuals concerned with medical innovation.

15. Specific improvements in the regulatory processes for drugs, diagnostics, medical devices and agriculture biotechnology.

The specific improvements needed in the regulatory process for devices are described in item #1 of the AdvaMed competitiveness agenda above. FDA needs better performance metrics focusing on total review time, not FDA time. It needs to streamline the IDE process. It needs to take the "least burdensome" requirements of existing law seriously. It needs to train reviewers and supervise them appropriately. It needs more device specific guidances and other mechanisms, such as regular and substantive meetings with applicants, to assure companies understand what is expected of them and that decisions are consistent. It needs to assure access to the best available advice and scientific information for review decisions.

AdvaMed wishes to thank OSTP for providing this opportunity to comment on this important issue and wishes, once again, to commend the President for identifying the importance of creating a National Bioeconomy Blueprint to secure America's economic future.

[1] The Lewin Group, "State Economic Impact of the Medical Technology Industry," June 7, 2010 and February, 2007.
[2] Ibid.
[3] *Ibid.*
[4] *Ibid.*
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[6] United States International Trade Commission, "Medical Devices and Equipment: Competitive Conditions Affecting U.S. Trade in Japan and Other Principal Foreign Markets," March, 2007.
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AdvaMed
Advanced Medical Technology Association

June 27, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number: FDA-2011-N-0259 – Periodic Review of Existing Regulations; Retrospective Review Under Executive Order 13563

Dear Sir/Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, we are pleased to submit these comments in response to the Food and Drug Administration's (FDA) review of regulations to assess whether they can be made more effective and less burdensome in achieving regulatory objectives.

AdvaMed is the largest medical technology association in the world. Our member companies produce the medical devices, diagnostic products and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. We applaud the spirit behind the President's Executive Order and, in particular, its emphasis on the need for the regulatory system to promote economic growth, innovation, competitiveness, and job creation while protecting public health, welfare, safety, and the environment.

Our industry has historically been an engine of job creation and economic growth. The jobs our companies create are good ones, with wages well above average both for the economy as a whole and even substantially above the average for other manufacturing sectors. We are one of the few manufacturing sectors with a consistently favorable balance of trade. America's medical technology industry is the acknowledged world leader.

While our industry has had a strong record of success, we are increasingly challenged in our efforts to maintain our leadership relative to other countries and to continue to provide economic growth in America. Our industry is more dependent than most on a favorable

government regulatory climate because we are so heavily intertwined with federal policy in so many ways. Particularly important for us are the policies of FDA. Every product we manufacture is regulated by FDA and most require pre-clearance or approval before they can be marketed.

As you develop your response to the President's Executive Order, we thought it would be helpful to identify for your consideration FDA rules affecting our industry that might be made less burdensome or altered in other ways to achieve the President's goals consistent with the agency's underlying responsibility. While the Executive Order only refers specifically to regulations, we have identified subregulatory rules since the impact of these rules on industry can be as important as rules established by formal rulemaking. In addition, we have included rules and policies that are currently under consideration or development as well as those already on the books.

FDA Identification of Areas for Less Burdensome Approach

Before we identify FDA rules which we believe might be made less burdensome, we would like to support and commend FDA for its identification of several medical device regulatory items in the Department of Health and Human Services' May 18, 2011 *Preliminary Plan for Retrospective Review of Existing Rules.* FDA identified three areas:

- Revise the Adverse Events reporting system to convert to a paperless, electronic reporting system. We agree this will help FDA more quickly review these reports and identify emerging public health issues.
- Continue its ongoing review of medical device classifications based on risks to determine whether particular devices can be reclassified to a lower level. FDA indicated that this would reduce burdens for industry while maintaining the safety and efficacy of the products.
- Allow validated symbols in certain device labeling without the need for accompanying English text. We agree with FDA that this change will reduce the burden of having unique labeling requirements for the U.S. market and achieve consistency with labeling requirements for international markets.

Identification of FDA Rules and Policies for a Less Burdensome Approach

Posting Device Labeling in an Online Repository

FDA is considering requiring posting all current device labeling in an on-line resource. Such a general requirement would be highly burdensome, potentially counterproductive for patients, and not improve patient safety. Devices are shipped with the most up-to-date information (labeling) needed by the healthcare providers and patients to safely and effectively operate the device. For some devices, safe operation of the device and its accessories requires training; labeling alone is not sufficient and reliance on a printed label alone could create hazards. Labeling relating to operation or programming of a device can be quite voluminous, intended for providers, and not only unhelpful but potentially misleading to patients. Finally, selecting the correct labeling from an online repository could be quite difficult given the number of similar devices and the rapid upgrading of devices. Incorrectly identifying the labeling associated with a device could create hazards for patients. Reliable

transmission of labeling information to an online repository would also likely require the use of an HL7 Structured Product Label (SPL) messaging standard. The SPL process is formulaic and very cumbersome, particularly as device labeling is very different and not nearly as standardized as drug labeling. AdvaMed does see benefit to patient users and family caregivers in a more uniform, recognizable access point on manufacturers' website for device labeling. To that end AdvaMed recommends the development and use of a branded "banner button" on manufacturers' website home pages to guide patient users and family caregivers to needed device labeling. Labeling information available through this link would be limited to safety-related elements, e.g. alarms and error messages, warnings, precautions, and contraindications; and patient user or family caregiver operating and maintenance instructions. The manufacturer labeling information webpage should also contain a toll-fee customer service telephone number and email address.

Eliminate Class I Reserved List

As a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA), all Class I devices are exempt from the requirement of premarket notification, unless the device is intended for a use that is of substantial importance in preventing impairment to human health or presents a potential unreasonable risk of illness or injury ("reserved" criteria). Therefore, only those Class I devices that meet the reserved criteria remain subject to premarket notification requirement. (See 63 FR 5387, February 2, 1998, for a listing of Class I "reserved" devices.) Many of these reserved devices do not present hazards that require premarket notification and, thus, their retention on the list creates an unnecessary burden for manufacturers and for FDA. FDA should determine that all devices remaining on the reserved list are exempt or FDA should reclassify them. This is consistent with FDA's plan to review medical device classifications based on risk.

Exemption of In Vitro Diagnostic Devices

As part of the qualitative goal commitments of the Medical Device User Fee and Modernization Act of 2007 (MDUFMA), FDA agreed to facilitate the development of *in vitro* diagnostic (IVD) devices and improve the premarket regulatory process for IVD medical devices through consideration of low-risk Class I and Class II IVD devices for exemption from pre-market notification. Similarly, AdvaMed agreed to identify suitable exemption candidates from among test systems that still require 510(k) clearance. As part of that effort, AdvaMed developed a systematic, risk-based process and provided those criteria and candidate IVDs to FDA. FDA has acknowledged that ever-increasing numbers of premarket notifications for IVDs, which require formal review under section 510(k) of the Food, Drug and Cosmetic Act (FD&C Act), are stretching their resources and leading to longer review times, thereby delaying the availability of important diagnostic tools. Preparation of 510(k) submissions for well-established, low-risk IVD test systems divert critical resources that could otherwise be dedicated to bringing new, advanced diagnostic markers and analytical technologies to the public. To ensure effective use of resources, FDA should now review the list of low-risk IVDs provided by AdvaMed and exempt suitable IVD devices from pre-market notification. Furthermore, FDA should consider similar exemptions for other devices being reviewed by the CDRH that are suitable for exemption in order to support the overall review process and promote less burdensome regulation that supports the

public health and innovation. Again, this is consistent with FDA's plan to review medical device classifications based on risk.

ClinicalTrials.gov Proposed Rule

FDA and the National Library of Medicine (NLM) are developing a proposed rule to implement portions of Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The statute directs FDA and NLM to determine whether to require disclosure of the full clinical trial protocol, whether to require disclosure of trials associated with unapproved/uncleared products, and whether to retroactively require trials conducted prior to the effective date of FDAAA to be entered in the databank. AdvaMed believes that current detailed disclosure requirements provide the needed information for clinicians and patients and that a requirement to disclose the full trial protocol would divulge confidential commercial information and would harm competitiveness without commensurate public health benefits. Similarly, disclosure of trial information associated with unapproved/uncleared products would divulge confidential commercial information and harm competitiveness with little public health benefit, since these products cannot be marketed. Existing regulations already require disclosure of trial results to patients that participated in the trial. AdvaMed supports (as indicated in our previous comments to the docket) disclosure of trial results for unapproved/uncleared products for the small subset of products whose trials were stopped for safety reasons. With respect to retroactive application of Title VIII requirements, it would be tremendously burdensome to require manufacturers to enter registry and results data for trials conducted prior to the effective data of FDAAA due to the time and resources required to compile the clinical trial information and revise it to fit the format required for the ClinicalTrials.gov database, with no apparent public health benefit.

Assurance Cases

In draft guidance issued in April 2010 titled *"Total Product Life Cycle: Infusion Pump – Premarket Notification [510(k)] Submissions,"* FDA is requiring all 510(k)s for infusion pumps to include assurance case reports for review. Such reports have never been used in the medical device industry. They also duplicate and require conversion of existing risk management information – required as part of the Quality System Regulation (QSR) (21 C.F.R. § 820) and pursuant to *ISO 14971 Medical devices – Application of risk management to medical devices* – into the assurance case format. Compliance with the QSR of medical devices cleared through the 510(k) pathway is typically determined through FDA's inspection process, not the FDA review process. In addition to unnecessarily requiring the conversion of existing information to the assurance case format, assurance cases can be challenging and burdensome to develop, to maintain and to reuse, and FDA has provided no guidance on acceptable assurance case approaches. Since the assurance case requirement was instituted over a year ago, only one infusion pump 510(k) has been cleared which signals the inherent challenges and difficulties associated with assurance case reports for medical devices. FDA is taking other steps to assure the safety and effectiveness of infusion pumps including an enhanced focus on pre-inspections and standards development involving key stakeholders and the additional assurance case requirement is unnecessarily burdensome.

Clinical Evaluations

FDA is requiring clinical evaluations for all new or significantly modified infusion pumps as a condition of clearance. Since legally-marketed infusion pumps are currently available, it may be very difficult to recruit patients for clinical evaluations of new ones. Moreover, clinical evaluations are not the best method for evaluating the safety problems with infusion pumps that FDA has identified. Such evaluations would create substantial, unnecessary burdens for manufacturers compared to alternative approaches. AdvaMed has recommended an alternative method to test infusion pumps that has been described as "real-use environment evaluations." Real-use environment evaluation protocols *would not* require pumps to be connected to a patient but *would* require clinicians to perform scripted tasks on the test device. Clinicians would be exposed to lighting and noise challenges, would be required to respond to audible alarms and would have scheduled and unscheduled interactions with the pump to test the user-device interface as the clinician programs complex drug regimens in the pump's intended environment (e.g., hospital). We believe this approach would meet FDA safety objectives in a less burdensome and more practical manner while facilitating expeditious patient access to safer infusion pumps.

Device Listing and UDI May Be Redundant

21 CFR § 807.25 delineates the "Information required or requested for establishment registration and device listing." Many of the data elements required by the Registration and Listing Rule (§ 807.25) are expected to be required by the Unique Device Identifier Rule, due to be published by June 30, 2011. Reporting the same information into two separate databases would be overly burdensome and unnecessary and FDA should assure that duplicative information is not required.

Malfunction Adverse Event Summary Reporting for Low-Risk Devices

Section 227 of FDAAA 2007 directed FDA to establish criteria for quarterly summary reporting of malfunction adverse event reports for Class I and Class II devices that are not permanently implantable, life-supporting, or life-sustaining. Nearly four years later FDA has yet to develop the criteria. In a March 8, 2011 Federal Register Notice on this topic, FDA advised manufacturers to continue to submit individual reports for these devices, and indicated it would, in the future, develop criteria for quarterly reporting through rulemaking. Such a process unnecessarily delays the implementation of this provision. The requirement to continue individual reporting of device malfunctions where Congress has already determined quarterly summary reporting is appropriate is unnecessary and burdensome. FDA should take immediate action to implement quarterly summary reporting for device malfunctions.

Medical Device Innovation Initiative

In February, 2011, the Center for Devices and Radiological Health released the *CDRH Innovation Initiative*.[1] We support FDA focus on fostering innovation to enhance patient

[1] These comments are intended to summarize AdvaMed's views on whether certain regulations or future regulations can be made more effective or less burdensome. It should be noted AdvaMed submitted comprehensive comments on the CDRH Innovation Initiative to Docket No. FDA-2011-N-0063.

care, and improve U.S. competitiveness but we believe several elements of the Innovation Initiative are off-track. AdvaMed has a number of recommendations to revise the elements of the proposal to make them more effective. Rather than investing limited FDA resources in developing a totally new and resource-intensive pathway for just one or two devices per year, CDRH should focus on incorporating elements of the Innovation Initiative into the existing expedited review process so that the expedited review process works as intended by Congress. For example, more devices could benefit if FDA implemented interactive review with an experienced review team, utilized external experts and utilized the resources and expertise of the Center Science Council (CSC) to make the expedited pathway work. In addition, the proposed eligibility criteria for the Innovation Pathway and for expedited review are nearly identical and as the Innovation Initiative report noted, only 23 applications have been accepted for expedited review in the 5-year period 2005 to 2010. AdvaMed recommends that the existing expedited review criteria be preserved.

AdvaMed also recommends against using limited CDRH resources to certify sites for device design/redesign and development. These sites would replicate what device manufacturers already do and the concept raises troubling conflict of interest questions. These sites would, in effect, compete with manufacturers to develop medical devices while having the full imprimatur of U.S. government support and approval. Finally, AdvaMed also questions whether it is the best use of CDRH's time and resources to develop a publicly-available core curricula – particularly given the large number of guidance documents that the Agency is committed to issuing this year and the ongoing need to update device-specific guidance. CDRH could instead restore the previous format and content of Device Advice which effectively operated as a core curricula. Unfortunately it is more difficult to find substantive and helpful content in the redesign of Device Advice on FDA's website.

510(k) Report Recommendations Referred to Institute of Medicine

When FDA issued its 510(k) and Science Report Recommendations it announced that several proposals would be referred to the Institute of Medicine for consideration. We understand FDA will seek additional public comment on any IoM proposals before deciding whether to implement any particular IoM proposal. Although it is not clear IoM will endorse any of the proposals, in the spirit of open communication, we offer the following comments on certain of the proposals referred to the IoM.[2]

Consolidation of the Terms "Indication for Use" and "Intended Use"

Consolidation of "intended use" and "indications for use" into a single term will result in many more NSE determinations and thus substantially increase the number of PMA applications. PMA applications require substantial company investment and resources and user fees associated with PMA applications are significantly higher. It is not clear there is

[2] These comments are intended to summarize AdvaMed's views on whether certain regulations or future regulations can be made more effective or less burdensome. It should be noted AdvaMed submitted comprehensive comments on FDA's 510(k) and Science Report Recommendations to Docket No. FDA-2010-N-0348.

any substantive public health benefit to consolidating the two terms but there is clear value in preserving the terms as separate concepts. "Intended use" broadly describes the use of a generic type of device (i.e., what the device does) while "indications for use" more specifically describes the device's clinical uses and patient population(s). Examples of intended use and indications for use include:

- The *intended use* of an electrosurgical cutting and coagulation device is to remove tissue and control bleeding by use of high-frequency electrical current (21 C.F.R. § 878.4400). Electrosurgical cutting and coagulation devices, however, may be specifically designed to accommodate different anatomies. They may have *indications for use* in thoracic, gynecologic, ENT, or other procedures, as illustrated by the 31 product classification codes for electrosurgical instruments.
- The *intended use* of an infusion pump is to deliver fluid to a patient in a controlled manner (21 C.F.R. § 880.5725). External infusion pumps may have any of the following *indications for use*:
    - general administration of drug solutions vs. blood vs. insulin.
    - intravenous, epidural, subcutaneous, subarachnoid, etc.
    - patient-controlled analgesia
    - hospital versus home use
- The *intended use* of a gas analyzer is to provide a means of monitoring gas concentration and to alert clinical personnel when limits fall outside of a pre-specified range (there are over 15 classification regulations for gas analyzers). The indications for use of a gas analyzer could be for an anesthetic agent, or oxygen, carbon dioxide, or nitrous oxide.

Combining the two terms may constrain the meaning of intended use, remove the flexibility that is currently afforded to the Agency in determining what new uses should be regulated within the confines of Section 510(k), and unnecessarily narrow the meaning of substantial equivalence. Indeed, combining the terms eliminates the distinction between "general" and "specific" uses that FDA has relied upon in determining whether the addition of a specific indication for use may trigger the need for additional data, including clinical data, and may necessitate the need for a PMA. FDA has recognized that the addition of a specific indication may or may not alter a device's intended use, depending on a multitude of factors. Furthermore, removing the "Indications for Use" terminology will result in confusion among patients and health care professionals who rely on the indications for use appearing in product labeling consistent with other FDA-regulated products. Consolidating the two terms could also delay patient access to new devices because of a potential increase in NSE determinations. We do not believe consolidation of the terms "intended use" and indications for use" is an effective use of FDA resources.

Expansion of Statutory Authority to Consider Off-Label Use When Determining Intended Use

FDA has indicated it should seek explicit statutory authority to allow FDA to consider possible off-label use when determining intended use. This would give FDA authority to require a company to develop and submit additional data for the potential "off-label" use in order to obtain FDA clearance or approval. This could be quite burdensome for companies

who would be required to develop data for an off-label use they never intended. Such a requirement could represent an undue hardship to a smaller company that does not have the economic means to pursue a use it did not intend. It may also result in the company's decision not to pursue commercial development of a new and potentially useful device or diagnostic, further stifling innovation. The existing statute provides a remedy for any FDA off-label concerns. CDRH has authority to require statements in the labeling including limitations within the intended use statement if there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device, and if such use could cause harm. This Congressionally-mandated path provides a more flexible path for CDRH to follow while protecting public health, and is less onerous for both the Agency and industry. Likewise, in the postmarket period, the Agency has the ability to deal with manufacturers that engage in off-label promotional activities. Specifically, 21 C.F.R. § 801.4 provides the Agency with considerable discretion in identifying off-label uses and company activities geared toward off-label promotion. When these situations arise, FDA can take many actions to stop off-label promotion and to encourage compliance with applicable requirements.

Requirement to Keep One Unit of a Device Available

FDA has proposed requiring each submitter to keep one unit of a device available for CDRH to access upon request. AdvaMed believes this is a burdensome proposal and it presents numerous practical challenges. Keeping a device available indefinitely so it can be examined when it is cited as a predicate is impractical for industry and would provide limited benefit. Providing the space necessary to ensure secure storage with appropriate environmental conditions would present a financial and logistical burden on industry, especially on small companies with limited facilities, with no commensurate benefit to public health. Indefinite retention of devices, especially IVD products, with limited shelf-lives would not provide an accurate representation of the device after the use-before date has passed. In some cases, minor changes are made to devices during their marketed life. Retaining a sample of each version of the device would add to the storage burden. AdvaMed recommends a much more limited approach that would enable CDRH to request (but not require) a submitter to provide a unit of the device only when seeing the actual device is necessary for determining substantial equivalence with the understanding that the device is used for education of the reviewer, is not appropriate for testing, and that the request does not delay the review of the submission.

Proposal to Issue Guidance to Create a Class IIb

CDRH proposed to develop guidance defining a subset of class II devices, called "class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would typically be necessary to support a substantial equivalence determination. AdvaMed believes that the scope of the products proposed by FDA for Class IIb is too broad and that the proposed requirements, when considered in their totality, are overly and unduly burdensome for Class II devices. AdvaMed recommended instead providing enhanced transparency and predictability for a very small, focused subset of Class II devices for which CDRH would provide advanced notice that additional information beyond that normally provided in a 510(k) may be expected to support a

substantial equivalence determination. The AdvaMed proposal provided suggestions for a number of additional submission requirements that could be required for a device in the subset but it **did not** recommend that all devices in the subset be required to comply with all enhanced requirements. Nor did it suggest that all devices for which CDRH currently requires clinical information automatically become members of the subset. In contrast to the FDA proposal, the AdvaMed proposal would not create a new classification scheme for medical devices in the United States but rather the development of risk-based guidance establishing standards and clear direction for certain device types within the current Class II program. Because these appropriately identified devices will require additional resources by both industry and FDA, it is important that they are limited to a small number of higher risk devices where public safety will benefit from the extra expenditure of resources, otherwise the extra requirements will not be practically implementable and will detract from the focus on the truly higher risk devices. We believe the AdvaMed proposal represents a less burdensome approach.

Seek Authority to Require Postmarket Surveillance Studies as a Condition of Clearance
FDA proposed obtaining broader authority to require condition-of-clearance studies. AdvaMed believes such authority is unnecessary and duplicative of existing authority in Section 522 and that it could lead to a proliferation of burdensome postmarket studies that fail to enhance public health. FDA may already request postmarket studies through Section 522 postmarket surveillance orders.

Implementation of Multiple Regulations/Policies/Guidances Simultaneously
In general, FDA should evaluate the impact of developing and implementing multiple changes to existing programs at the same time. AdvaMed is concerned FDA does not have the resources to effectively implement all of the program changes it has recently proposed such as the 510(k) and Science Implementation Plan initiatives, the Innovation Initiative, and purported upcoming changes to the PMA program. The disruption caused by "changing the rules" across so many programs can be burdensome and lead to inefficiencies and errors by both agency staff and industry. It will also further slow an already unacceptably slow review process due to the diversion of resources. FDA should create and implement change in a structured manner that does not place additional burden on the existing work flow. New and modified requirements always result in a period of adjustment and implementation of several changes at the same time can simply multiply the inherent problems.

Color Additives Used in Medical Devices
The FD&C Act states that devices containing a color additive are considered unsafe, and thereby adulterated, unless a regulation is in effect listing the color additive for such use. The FD&C Act limits applicability of these provisions to color additives that directly contact the body for a significant period of time. At the present time, "significant period of time" is not defined by FDA regulation. Current CDRH policy does not consider the period of time a color additive is in contact with the body and therefore typically requires maximum test data for the use of color additive for all uses (e.g., both contact that is measured in minutes and long-term contact through an implanted device), which often consists of thousands of pages of data. Color additive petitions are filed with CDRH and processed by CFSAN. Current

FDA processes and requirements fail to clearly delineate color additive roles and responsibilities assigned to CDRH and/or CFSAN. As a result, color additive petitions languish for years. Section 706 of the Act and 21 CFR Parts 73 and 74 should be reviewed and revised to ensure the less burdensome approach to evaluating the safety of color additives used in medical devices.

Posting of Untitled Letters on FDA Website

FDA announced on May 26, 2011 that it will expand disclosure of Untitled Letters on its website by the end of 2011. AdvaMed commented previously and continues to believe that posting of this information is not an effective use of FDA resources and has little public health value. FDA issues Untitled Letters when it is unclear that a practice is violative or that it presents a public health threat. They may be issued for minor violations or where the line between what is acceptable and what is violative is unclear. Disclosing Untitled Letters effectively elevates them to the status of Warning Letters and impugns a company's products or practices where no clear violation or public health issue exists.

Searchable Inspections Database

FDA announced on May 26, 2011 that it will include a searchable inspections database that includes the names and addresses of inspected facilities, inspection dates, final inspectional classification and a summary of common inspectional observations of objectionable conditions or practices found during inspections. AdvaMed commented on this initiative previously and continues to believe it is not an effective use of FDA resources and that it will have adverse consequences on companies with little public health value. We believe foreign regulators will misunderstand the inspectional classification and will inappropriately exclude products from their market or will take inappropriate punitive action against companies and that it will be inappropriately used for litigation purposes. We also believe the lay public may misinterpret the significance of Voluntary Action Indicated (VAI) inspectional findings. AdvaMed recommends that the searchable inspectional database be limited to Warning Letter recipients only (i.e., Official Action Indicated [OAI] inspectional classifications). Such letters are already available on FDA's website. Warning Letters identify a clear regulatory threshold. This threshold does not exist for VAI or No Action Indicated (NAI) inspection classifications. Where inspections result in no objectionable conditions or the objectionable conditions do not meet the threshold of regulatory significance there is little public value in disclosing the information. Finally ensuring accurate and up-to-date maintenance of yet another website will consume FDA resources without adding commensurate public health benefits.

CMS Collaboration with the FDA

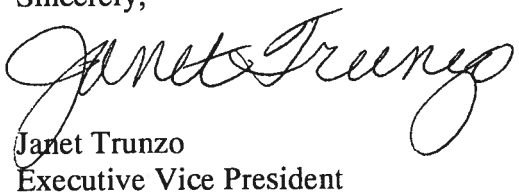
The scope and timing of collaboration between CMS and the FDA has been an ongoing area of concern for AdvaMed. The two agencies are currently considering guidance on "parallel review" of device marketing applications. AdvaMed believes very strongly that any parallel review envisioned by FDA and CMS should be triggered only at the request of the individual submitting manufacturer. Further, both agencies have separate and distinct missions. To this end, strong safeguards must be included to ensure that CMS only makes coverage determinations pursuant to its statutory mission of determining what is "reasonable and

necessary" for Medicare beneficiaries and not attempt to replicate FDA's role of determining what is "safe and effective." Conversely, safeguards should be implemented to ensure that FDA continues to determine what is safe and effective and not require that products provide outcomes evidence designed to support Medicare coverage decisions in order to receive marketing clearance or approval. One potential outcome of the proposed parallel review program is that companies would be required to conduct clinical trials that will support both FDA and CMS determinations. Designing and conducting medical device clinical trials that can support both FDA's (safety and effectiveness) and CMS' requirements (reasonable and necessary) is extremely difficult, if not impossible, and therefore, overly burdensome and should only be done at the request of the individual manufacturer.

Conclusion

Thank you for considering these comments. We hope they are helpful as you respond to the President's Executive Order and seek to achieve our mutual goal of effective and less burdensome regulatory policies that promote economic growth, innovation, competitiveness, and job creation while protecting and promoting the public health.

Sincerely,



Janet Trunzo
Executive Vice President
Technology and Regulatory Affairs

VIA E-MAIL TO BIOECONOMY@OSTP.GOV

December 6, 2011

Office of Science and Technology Policy
Executive Office of the President
725 17th Street, Room 5228
Washington, DC 20502

Response to Request for Information: Building A 21st Century Bioeconomy

Ladies and Gentlemen:

The University City Science Center, located in Philadelphia, Pennsylvania, hereby submits this letter in response to the Request for Information on Building a 21st Century Bioeconomy, issued by the Office of Science and Technology Policy. As a member of the US Department of Commerce's Innovation Advisory Board, I am pleased to share with you the Science Center's recommendations for harnessing biological research innovations to meet national challenges in health, food, energy, and the environment while creating high-wage, high-skill jobs.

We believe that research parks, business incubators, and other technology-based economic development organizations, such as the Science Center, can serve as innovation intermediaries or linchpins to connect – without any bias or favoritism – the creators of emerging technologies, located at research institutions, with the investors and funders of the development of these technologies, located at venture capital firms and industrial companies, in order to maximize the value of early-stage technology generated by researchers and accelerate technology commercialization.

In this response, we will focus on (a) suggestions for making specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs that would help accelerate commercialization of federally-funded bioeconomy-related research, including the presentation of a proposed model for bringing together academic and commercial resources at an earlier stage in order to advance SBIR/STTR-funded research more rapidly; and (b) suggestions for building new, high-impact public-private partnerships to facilitate the commercialization of life sciences research, including a discussion of the Science

Center's QED Proof-of-Concept Program – the nation's first multi-institutional proof-of-concept program in the life sciences.

Background on the University City Science Center

Established in 1963, the Science Center is the oldest and largest urban research park in the United States. Our mission is to support business incubation, technology commercialization, and technology-based economic development. Our 31 shareholders include many of the distinguished colleges, universities and research institutions located throughout Pennsylvania, New Jersey and Delaware. (Attached as Appendix A is a list of the Science Center's shareholders.) Our Board of Directors includes both academic and non-academic officials from many of these institutions, as well as representation from science and technology companies, investment and venture capital firms, and economic development organizations.

Situated in West Philadelphia, adjacent to the University of Pennsylvania and Drexel University, the Science Center campus includes 2.0 million square feet of laboratory, office and medical facilities. The Science Center accelerates technology commercialization and the market availability of life-enhancing scientific breakthroughs by bringing together innovations, scientists, entrepreneurs, funding, laboratory facilities and business services. We provide an unparalleled regional resource center designed to inspire a community of knowledge, spark the spirit of enterprise, and help expand and strengthen the region's technology sector; and we offer a steady stream of networking, professional and product development, and entrepreneurial support programs designed to leverage the rich resources available on our campus and throughout the region.

The work of the approximately 100 incubator and established companies that currently call the Science Center home ranges from information technology, nanotechnology and green technology to cognitive science, biotechnology, bioinformatics, diagnostics, healthcare and medical devices. According to a study by the Economy League of Greater Philadelphia,[1] of the more than 350 organizations that have been incubated on the Science Center campus since our inception in 1963, 93 remain in the region. Currently, these companies directly employ more than 15,000 people at an average salary of $89,000, and they, along with our incubator residents, contribute more than $9 billion to the regional economy annually.

Graduates of the Science Center's incubation programs include Centocor (acquired by Johnson & Johnson, and now known as Janssen Biotech), BioRexis (acquired by Pfizer), and Avid Radiopharmaceuticals, which has pioneered a medical imaging method to detect beta amyloid plaques for the diagnosis of Alzheimer's disease. Avid entered the Science Center's incubator in 2005, graduated in 2009, and was acquired by Eli Lilly in 2010 for $300 million in cash up front,

[1] The University City Science Center: An Engine of Economic Growth for Greater Philadelphia (2009), prepared by the Economy League of Greater Philadelphia. Available online at www.sciencecenter.org.

plus an additional $500 million in future payments based upon the achievement of defined milestones.

Partnering with research institutions, entrepreneurs, funders, industry leaders, governmental agencies at all levels, and economic development organizations across Pennsylvania and beyond, the Science Center continues to help move technology out of the lab and into the marketplace, where it can benefit the region and the world.

Copies of the Science Center's 2011 Annual Review and our recently published economic impact study, "The University City Science Center: An Engine of Economic Growth for Greater Philadelphia," are available for download at www.sciencecenter.org.

I. RECOMMENDATIONS FOR CHANGES IN SBIR AND STTR PROGRAMS

SBIR/STTR is a valuable source of funding for supporting high-risk research and development being conducted by small businesses, where the goal is to invest in new product development. In the life sciences, three agencies are important sources of SBIR/STTR funding: the National Institutes of Health, the National Science Foundation, and the Department of Defense.

While historically, existing small businesses may have utilized SBIR/STTR funding to explore new product concepts for their pipelines, in a climate where private investment is scarce and investors are placing more emphasis on rapidly and efficiently developing marketable products, small businesses are less inclined to dilute their focus. Consequently, there is increasing potential for SBIR/STTR funding to be used as a source of start-up or seed capital by new companies rather than as a source of follow-up product financing by existing small businesses. However, SBIR/STTR funds are ill-suited for new venture creation because of eligibility limitations, operating policies, and goals and metrics of performance. We believe that there are opportunities for SBIR/STTR programs to be utilized more effectively for product development by newly-launched small businesses, particularly those that are focused on developing technologies licensed from federally-funded institutions.

Limitations of SBIR/STTR for New Venture Formation

SBIR and STTR programs can be a critical source of funding for bridging the gap between basic research funding and private sector investment financing. However, SBIR/STTR funding pools are becoming increasingly competitive, and even when successfully obtained, SBIR/STTR funding is often not sufficient to maximize the likelihood of new startups becoming scalable small businesses.

In 2010, through a series of working groups, the Science Center's Scientific Advisory Committee (SAC), composed of representatives of major federally-funded research institutions

in the Greater Philadelphia region, private-sector companies, and other stakeholders, collectively considered the issue of forming new start-up companies using SBIR/STTR funding. While affirming the importance of the mechanism, these groups identified several challenges:

- The need for a commercial entity: To attract funding and expertise, there is often a need for a commercial entity. Many (although not all) high-potential scientific projects are simply too early-stage to justify the creation of a dedicated corporate entity – and there are few mechanisms by which to determine their appropriateness for a start-up company in advance.

- The need for additional funding: SBIR/STTR funds (typically $150,000 in Phase 1) are usually not sufficient to create a new, functioning commercial entity. This need is compounded by the inefficiencies that arise from duplicating infrastructure and administration for each separate entity.

- The need for additional expertise: Many projects are staffed primarily or solely by inventors. In the case of institutional inventors, there is a need for non-institutional staff to operate or manage the commercial for-profit program in order to avoid conflict of interest. In all cases, there is a need to build management and advisory structures, a difficult task for pre-capitalized start-ups.

The SAC working groups concluded that while many technologies are appropriate for individual start-ups, there is also a need for a consolidated mechanism that would enable technology managers to "road-test" early-stage technologies and to aggregate resources and expertise prior to launching new companies.

Proposed New Concept: Phase 1 Ventures

Following recommendations from the SAC and further investigation, including a large amount of external benchmarking using interviews with more than 20 opinion leaders within and outside the region, and drawing on primary research and experience in the field, the Science Center has developed the concept of Phase 1 Ventures (P1V).

P1V involves a partnership between a for-profit (SBIR/STTR-eligible) entity and one or more non-profit entities that are sources of technologies. Other strategic partners include economic development organizations, investors and entrepreneurs, and corporate entities. The partnership approach enables the following critical ingredients to be connected:

- Technologies, typically developed using federal basic research funding

- A corporate entity enabling independent product development

- Commercial guidance
- Market input and capital
- Third-party management of academic, new company, and market interaction

P1V provides an independent, turnkey option that enables high-potential federal laboratory or university technologies to be road-tested, using Phase 1 SBIR/STTR or other seed-stage funding, for their suitability as foundations of new small businesses.

The P1V model offers all of the following:

- Assistance in the development of competitive SBIR/STTR funding applications for selected technologies.
- Projects that receive Phase 1 funding will be co-housed within a dedicated partnership – operated by an intermediary economic development organization such as the Science Center – which will include managers, staff, facilities, and resources to be provided to each project as needed to complete the Phase 1 work.
- Upon successful receipt of Phase 2 funding, new small business entities will have sufficient capital to attract dedicated resources and ultimately "graduate" from the accelerator.
- P1V will realize value and create a framework for sustainability through equity in the resulting small businesses that are launched through its process.

The P1V model presents a number of attractive features compared with traditional *ad hoc* venture formation:

- P1V provides an independent and collaborative pre-review process at the "point-of-invention" for screening and selecting projects that are suitable for SBIR/STTR funding and for eventual transition into fundable new companies.
- P1V exploits economies of scale by sharing fixed costs among multiple projects during their time in the shared P1V partnership.
- Advisory support in determining strategy and in managing R&D will lead to more successful Phase 2 SBIR/STTR grant applications and eventual private investment.

- Management and the accumulation of resources can be achieved in a strategic multi-step process (e.g. starting with interim management that can oversee multiple projects), avoiding the over-burdening of fragile new companies too early.

- By establishing a network of advisors and partners, P1V will facilitate connection of new companies with networks and private sector investors.

II. RECOMMENDATIONS FOR PUBLIC-PRIVATE PARTNERSHIPS

We believe that the highest impact opportunities for public-private partnerships relating to the bioeconomy are public-private partnerships that enhance or assist with the translation and commercialization of undeveloped, or underdeveloped, early-stage research at academic laboratories, federal laboratories, and private-sector companies.

In the context of technology commercialization, the "valley of death" refers to the barrier between early-stage technology and follow-on development in the private sector. Particularly in recent years, private capital for R&D has moved steadily "downstream," as investors and corporations favor later-stage, lower-risk technologies. This leaves many early-stage technologies, the supply of which has actually increased (as manifested by the number of scientific papers, invention disclosures, and patent applications), stranded in the laboratory. The question is: as the pipeline of biomedical products "dries up," how will the development of new products be sustained? This issue is currently receiving greater attention, as public policymakers and economic development organizations consider new ways to generate more value from the billions of dollars that are allocated to universities each year in research grants, and to unlock the value inherent in early-stage technologies at "big pharma" companies that are not being pursued due to reduced R&D operations or (in their view) insufficient potential return on investment.

Science Center's QED Proof-of-Concept Program

In 2009 the Science Center launched the nation's first multi-institutional proof-of-concept program to fund early-stage academic research projects in the life sciences and to promote the commercialization of the technologies resulting from those projects. Our program – named "QED," after the Latin phrase "*quod erat demonstrandum*" or "proven as demonstrated" – provides funding and business advice for academic researchers throughout the Greater Philadelphia region who are developing early-stage life science technologies with high commercial potential. QED helps promising researchers translate their publicly-funded basic research into privately-funded technology commercialization and product development opportunities. As angel investors, venture capitalists, and established companies increasingly shift their investments to later-stage initiatives, QED fills a critical gap in the innovation and funding pipeline.

The Science Center created QED in response to a 2007 study conducted by the CEO Council for Growth, an affiliate of the Greater Philadelphia Chamber of Commerce, which recommended the establishment of a proof-of-concept research fund to bridge the gap between research grants and seed funding.[2] The goals of the program are to engage the region's academic institutions, research scientists, entrepreneurs, investors, and industry in early-stage commercialization, and ultimately to increase the pace and value of technology transfer in the region.

QED leverages the Science Center's relationships with universities, healthcare institutions, public and private companies, and government agencies, driving technology transfer and new business formation, advancing entrepreneurship, and encouraging innovation, competitiveness, and knowledge-base retention and expansion. The program's key operating principles for technology commercialization are (a) to focus existing regional resources on substantially reducing early-stage business risk, and (b) to evaluate and position early-stage technologies for follow-on investment by established life science companies and private investors, thereby reducing the proliferation of sub-scale, undercapitalized ventures already in the market. Ultimately, the success of the program will be judged according to the metrics of technology transfer, including new venture formation, license execution, and outside investment.

QED provides key resources, including business guidance, bridge funding, and access to industry and investor representatives, to competitively selected projects. Currently, a total of 19 research institutions throughout the tri-state region participate in the program. Funding decisions are made by a regional selection team composed of representatives from pharmaceutical, medical device and medical diagnostics companies, private equity and venture capital firms, and economic development organizations. Each project selected for funding receives up to $200,000 over 12 months, with half of the funding provided by the Science Center and the other half by the scientist's host institution.

To date, QED has received and evaluated more than 227 proposals; proof-of-concept plans have been developed, with the assistance of business advisors, for 40 life science technologies at 15 institutions; 12 projects at eight institutions have received or been offered funding; and five of the funded projects have resulted in the licensing or optioning of technologies to the private sector, either through start-up or established companies. These early successes demonstrate the program's potential for meaningful impact on the region's innovation ecosystem through the collective engagement of academic, private sector, and entrepreneurial stakeholders, as well as a pipeline of new technologies that could significantly contribute to human health.

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[2] Accelerating Technology Transfer in Greater Philadelphia: Identifying Opportunities to Connect Universities with Industry for Regional Economic Growth (2007), prepared by the CEO Council for Growth. Available online at www.selectgreaterphiladelphia.com

Attached to this application are a list of the participating institutions in the program (Appendix B), a list of the companies and investment firms represented on the QED selection team (Appendix C), and a list of the nine projects funded to date, indicating the five projects whose technologies have already been licensed or optioned (Appendix D). One of the licensed technologies represents the first example of technology from The Children's Hospital of Philadelphia, the nation's oldest hospital for children, being commercialized via start-up company formation.

In addition to the direct benefits of commercial guidance (and, potentially, funding) received by successful applicants, there is also a benefit derived by the business advisors and student fellows through the collaborative and entrepreneurial learning experience. Not only are we working to develop a network of science and technology entrepreneurs – we are also creating an environment that encourages meaningful interaction between academic and commercial interests, resulting in (a) the provision of earlier commercial guidance to research technologies, (b) the creation of avenues for experienced entrepreneurs to identify new opportunities, and (c) the opportunity for students to gain real life, valuable experience in entrepreneurship.

More immediate indicators of success include:

- Evaluation and feedback to non-funded projects, better positioning them for funding from other programs

- Re-direction of limited resources from projects that prove to be unsuitable for commercial development

- Assembly of a comprehensive regional inventory of life science technologies with potential commercial value, creating a pipeline of commercially-evaluated technologies that are capable of bridging the "valley of death"

Longer-term indicators of success will include:

- Increased number of direct and indirect jobs, and per-capita wealth

- Development of new life science products which will improve the quality and efficiency of healthcare

The ultimate success of the QED program will be determined by the transfer of successful R&D proof-of-concept projects to the private sector. Meanwhile, program participants will continue to "learn by doing," to improve process productivity with each cycle, and to establish the basis for program continuation and scale-up.

QED as a Model for Public-Private Partnerships

We believe that our QED program can serve as an innovative and promising model for public-private partnerships nationwide:

- **QED serves a tri-state "regional innovation cluster."** The Greater Philadelphia region is one of the top metropolitan areas in the nation for research and development in the life sciences. QED is a collaborative program that extends across the region, transcending state and local boundaries. The program catalyzes the transfer and commercialization of early-stage life science technologies emanating from universities, hospitals and research institutions throughout 11 counties in Pennsylvania, New Jersey and Delaware. As a hub of innovation, entrepreneurship and technology commercialization in the region – without any mandated allegiance to a particular state or locality, and without any limitations or restrictions imposed by government (or any other third party) on where we can operate or whom we can assist – the Science Center is a neutral intermediary organization that can bring the region's institutions and other assets together in order to produce tangible results that benefit all.

- **QED is multi-institutional.** QED began in April 2009 with 10 participating research institutions; the number of participants has since expanded to 19. Cooperation and competition among the institutions serve to increase the regional technology pool and leverage regional resources more effectively, ultimately maximizing the program's impact. Also, the broad range of institutional participants aligns well with the Science Center's role as a facilitator of the region's dominant "innovation ecosystem" in the life sciences. Although other organizations elsewhere in the country – notably MIT and the University of California at San Diego – offer similar business advisory and funding resources, their reach is limited to projects at the host institution. QED's multi-institutional scope features a diversity of institutional sizes and characteristics within a versatile program model that minimizes administrative overhead. We believe that this model can be readily adapted to other regions in the US.

- **QED leverages existing multi-disciplinary resources.** QED builds upon the Science Center's extensive relationships with research centers, tech transfer offices, entrepreneurs, investors, public and private companies, and economic development organizations in order to address the multiple aspects of commercialization for all projects that enter the program. In particular, third-party scientific and commercial guidance is a critical component of QED. This guidance takes the form of business advice from experienced investors, entrepreneurs and industry representatives; technical and clinical review of technology by outside scientific reviewers; and market-based screening and selection teams that evaluate the projects with a focus on both the potential for follow-on investment and the anticipated market demand for the end-stage product.

- **QED is collaborative.** QED, by its nature, is a program that not only encourages, but demands, multidisciplinary collaboration between and among its participating institutions, principal investigators, business advisors, scientific reviewers, screening and selection team members, and prospective follow-on funders, thereby maximizing the prospects for high-quality, early-stage research with substantial end-stage market potential. It is this comprehensive approach that sets QED apart. Our intention is to organize and deploy the wealth of scientific, technological, and entrepreneurial talent and resources within our region – which transcend institutional, city, county, and state boundaries – towards a common goal of more efficient and effective life science commercialization.

- **QED strengthens an existing regional research capability.** A May 2009 report by the Milken Institute ranks the Greater Philadelphia life sciences "cluster" second among the 11 top life sciences clusters in the United States.[3] The Greater Philadelphia region's institutions of higher education excel at attracting research dollars; according to one study, the region attracted $1.5 billion in academic R&D funding in 2005, 62 percent of which was devoted to life sciences, followed by engineering and physical sciences.[4] That investment is paying off: the region averages 520 invention disclosures a year, surpassed only by Boston.[5] However, our region's universities and other research institutions are not achieving their full potential when it comes to economic development through entrepreneurship. QED is using technology transfer to spur economic development by successfully linking early-stage research with later-stage technology development and commercialization.

- **QED leverages funding from multiple public and private sources.** Currently in the fourth cycle of its pilot phase, QED has received funding from the US Department of Commerce's Economic Development Administration (EDA), the Commonwealth of Pennsylvania's Ben Franklin Technology Development Authority, the William Penn Foundation, and the Science Center's real estate development partner, Wexford Science + Technology. This funding is being leveraged by funding from the Science Center and the participating institutions. A total of $2.4 million has been committed by the Science Center and the participating institutions during the QED pilot phase, to cover costs incurred by award recipients in connection with funded projects. The Science Center continues to seek additional funding from Federal agencies and other government

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3 The Greater Philadelphia Life Sciences Cluster 2009: An Economic and Comparative Assessment (2009), published by the Milken Institute. Available online at www.milkeninstitute.org

4 Accelerating Technology Transfer in Greater Philadelphia . . . (2007). See Note 2.

5 Ibid.

sources, as well as additional funding from private sources in order to increase (and leverage) the economic impact of any public dollars invested.

- **QED is designed to be self-sustaining.** The Science Center is committed to continuing to move the QED program forward. Participating research institutions have each committed $100,000 of matching funds to any project submitted from their institution that is selected for funding. The Science Center and the participating research institutions have negotiated a share in licensing revenues and company equity that arise from successful QED projects. However, it is anticipated that long-term sustainability will require the formation of an endowment. Public policy changes should be instituted that would ease the current burden of financing this program until an endowment is substantially funded. Ultimately, we anticipate that demonstration of the program's success will encourage support from corporate partners. This process could be accelerated by providing tax incentives for private investment.

For all of the foregoing reasons, we believe that new, innovative public-private partnerships like our QED Proof-of-Concept Program represent a new paradigm for technology development, in which neutral "innovation intermediaries" like the Science Center can serve as facilitators. These intermediaries can uniquely promote greater collaboration and dialogue among the various stakeholders in the technology transfer process, which are essential to accelerating the commercialization of life science breakthroughs out of the lab and into the marketplace. They can also help to align often-mismatched incentives and cultural differences between academia and industry, creating an environment that supports the successful flow of R&D from basic research, through proof-of-concept projects, to product development and technology commercialization.

Importantly, the opportunity exists to scale up, expand and/or translate the QED program to other parts of the nation; to other sectors of the technology economy, such as energy and cleantech; to large companies with specific needs no longer supported by their own R&D capabilities; and to federal laboratories with under-commercialized research output. Organizations – such as the Science Center – that have a proven track record in technology commercialization can be utilized as reference points, in order to develop a national model for efforts to accelerate commercialization.

Conclusion

This letter describes two models for expediting the commercialization of early-stage technologies. These models leverage existing resources, address sustainability, and, importantly, are scalable and transferable. Federal agencies should encourage organizations that are working on similar initiatives to work together in a meaningful collaborative process that will allow funding to be more effectively deployed, thereby increasing the likelihood of successful outcomes. These outcomes will include the creation and growth of high-tech companies, high-

paying jobs, and high-demand medicines, medical devices and other technologies that, in turn, will fuel economic development in the United States and beyond. Regional innovation clusters and similar regional strengths can be emphasized, and appropriate incentives to collaborate and communicate can be provided, in order to foster an environment that facilitates the productive exchange of ideas and technologies.

Please feel free to contact me if you have any questions or comments on this letter or the attachments, or if you would like any additional information. In addition, I would be happy to meet with you at your convenience to discuss our ideas and programs in more detail, and I invite you to visit us here at the Science Center in Philadelphia to tour our facilities and learn more about who we are and what we do to support technology commercialization and economic development in the Greater Philadelphia region.

Thank you for your consideration.

Sincerely,

Stephen S. Tang, Ph.D., M.B.A.
President & CEO

APPENDIX A

List of Shareholders of University City Science Center

The American College, Bryn Mawr, PA
Bryn Mawr College, Bryn Mawr, PA
Burlington County College, Pemberton, NJ
The Children's Hospital of Philadelphia, Philadelphia, PA
Delaware State University, Dover, DE
Drexel University, Philadelphia, PA
East Stroudsburg University, East Stroudsburg, PA
Haverford College, Haverford, PA
Lafayette College, Easton, PA
Lehigh University, Bethlehem, PA
Lincoln University, Chester County, PA
Mercy Health System, Conshohocken, PA
NUS America (National University of Singapore), Philadelphia, PA
The Penjerdel Council, Philadelphia, PA
Pennsylvania Hospital, Philadelphia, PA
Philadelphia College of Osteopathic Medicine, Philadelphia, PA
Philadelphia University, Philadelphia, PA
The Presbyterian Foundation for Philadelphia, Philadelphia, PA
Rowan University, Glassboro, NJ
Rutgers, The State University of New Jersey, New Brunswick, NJ
Salus University (former Pennsylvania College of Optometry), Elkins Park, PA
Swarthmore College, Swarthmore, PA
Temple University, Philadelphia, PA
Temple University School of Podiatric Medicine, Philadelphia, PA
Thomas Jefferson University, Philadelphia, PA
University of the Arts, Philadelphia, PA
University of the Sciences in Philadelphia, Philadelphia, PA
University of Delaware, Newark, DE
University of Pennsylvania, Philadelphia, PA
Villanova University, Villanova, PA
Widener University, Chester, PA

APPENDIX B

List of QED Participating Research Institutions

The Children's Hospital of Philadelphia, Philadelphia, PA

Delaware State University, Dover, DE

Drexel University, Philadelphia, PA

Fox Chase Cancer Center, Philadelphia, PA

Harrisburg University of Science and Technology, Harrisburg, PA

Lankenau Institute of Medical Research, Wynnewood, PA

Lehigh University, Bethlehem, PA

Monell Chemical Senses Center, Philadelphia, PA

Philadelphia College of Osteopathic Medicine, Philadelphia, PA

Philadelphia University, Philadelphia, PA

Rutgers University, New Brunswick, NJ

Temple University, Philadelphia, PA

Thomas Jefferson University, Philadelphia, PA

University of Delaware, Newark, DE

University of Medicine and Dentistry of New Jersey, Newark, NJ

University of Pennsylvania, Philadelphia, PA

University of the Sciences, Philadelphia, PA

Widener University, Chester, PA

The Wistar Institute, Philadelphia, PA

APPENDIX C

List of Organizations Represented on QED Selection Team

Angiotech Pharmaceuticals

AstraZeneca

Becton Dickinson

Ben Franklin Technology Partners of Southeastern Pennsylvania

Blue Highway

Bristol-Myers Squibb

BioAdvance

Bracco

Delaware Crossing Investors Group

Exponent

FemmePharma

Integra Life Sciences

Johnson and Johnson

MentorTech Ventures

Merck

MidAtlantic Angel Group

NewSpring Capital

Novartis

Osage University Partners

Quaker Partners

Safeguard Scientifics

Seguro Surgical

Sigma Aldrich

SR One (GSK)

APPENDIX D

Projects Selected for QED Funding

Project	*Institution*	*Technology*
Near infrared wound monitor #	Drexel Univ.	Diagnostic device
Breast cancer detector #	Drexel Univ.	Diagnostic device
Sol-gel drug delivery platform	Univ. of Penn.	Combination therapy
Magnetic nanoparticle drug delivery system ~	Children's Hospital	Combination therapy
Heart valve replacement system	Univ. of Penn.	Implantable device
U1 adaptor for gene silencing #	Rutgers Univ.	Therapeutic/research
Differentiation therapy for leukemia~	Temple Univ.	Therapeutic
miRNA cluster to treat HCV	Children's Hospital	Therapeutic
Nanopore system for detection of miRNAs	Univ. of Penn.	Diagnostic device

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Technology licensed

~ Technology optioned

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December 5, 2011

Office of Science and Technology Policy
Executive Office of the President
725 17th Street Room 5228
Washington, DC 20502

RE: Office of Science and Technology Policy Request for Information: Building a 21st Century Bioeconomy

To Whom It May Concern:

I offer these comments on behalf of Food & Water Watch, a national nonprofit consumer advocacy organization, on the Office of Science and Technology Policy's (OSTP) request for information as it develops the Building a 21st Century Bioeconomy Blueprint. We appreciate this opportunity to provide input on the Administration's goals for harnessing emerging biotechnology in order to mitigate national health, food, energy and environmental crises. We urge the Administration to ensure that these emerging technologies are properly evaluated before reaching the market.

On September 16, 2011, President Obama announced a suite of initiatives to fast-track "ideas from the lab to the market." One such initiative is the Administration's charge to draft a "Bioeconomy Blueprint," using novel biotechnologies to supposedly solve some of the health and environmental challenges of our day.

As described by the Administration, the "Blueprint will focus on reforms to speed-up commercialization and open new markets, strategic research and development investments to accelerate innovation, regulatory reforms to reduce unnecessary burdens on innovators, enhanced workforce training to develop the next generation of scientists and engineers, and the development of public-private partnerships." We will take this opportunity to address some of the specific questions posed by the OSTP. In addition, we see this RFI as an opportunity to discuss the Administration's duty to act with caution in considering these emerging technologies so as to protect human health and the environment.

In response to question 2, "what should be the federal funding priorities in research technologies, and infrastructure to provide the foundation for the bioeconomy," we believe that it is most prudent to devote federal funding to the development and testing of improved risk assessment tools that can adequately determine the risks posed by emerging biotechnologies. New risk tools are an imperative first step toward understanding the safety and prudence of commercializing new technologies.

The second funding priority must be environmental health and safety (EHS) research. EHS research must be done before attempting to commercialize whole technologies. We urge the Administration to learn from historical examples of hasty decision-making in the commercialization of unsafe chemical, pharmaceutical and technological products.

To further clarify, we fundamentally oppose the push for commercialization of emerging biotechnologies at this time. In answer to question 5, "what are the barriers preventing biological research discoveries from moving from the lab to commercial markets," we argue that the main barrier is, and should be, the unknown human and environmental health impacts of said technologies.

For example, scientists do not yet know how to accurately assess the risks associated with using nanotechnology on the consumer market. Conventional risk assessment tools appear to be far too blunt for materials that behave differently and pose novel exposure pathways than their larger counterparts. Before commercialization can take place new risk assessment tools must be generated and used for every novel product added to the market.

The additional barrier of having a broken regulatory system that is incapable of governing emerging technologies is problematic as well. .

We also oppose the Administration's "experimentation with private-sector led models for funding the commercialization of life sciences research." Life sciences research should, as much as possible, be performed by independent scientists who are not in anyway obligated to private interests for funding, career advancement, or publication of their work.

In response to question 8, "what are the challenges associated with existing private-sector models for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges," we would argue that it is far too soon to answer this question. A more appropriate question is one that asks how to appropriately regulate the products that will come from a bioeconomy. Agencies should be collaborating on generating and testing new risk assessment measures in addition to drafting new statutes that will create a more appropriate regulatory regime that can begin to address the risks of these technologies.

We are especially concerned about the Administration's focus on "reducing regulatory barriers to the bioeconomy" illustrated in questions 13-15. Using nanotechnology as an example, nanomaterials are already on the consumer market even though nano-specific regulations do not exist. The Administration's focus on reducing regulatory barriers is laughable considering there is already an obvious absence of oversight and a complete failure to require technological application disclosure to consumers. More to the point, this is a dangerous and desperate approach to solving our economic problems.

With respect to improving transparency as asked in question 14, agencies must make safety and efficacy data accessible to the public. And, the Administration must draft and enforce consumer-labeling laws. Consumers deserve disclosure when choosing between novel and conventional products.

Public-private partnerships are *not* a solution to the challenge of funding life sciences research. Public-private partnerships do *not* reduce costs; they are expensive to implement and can lead to job loss.

Furthermore public-private partnerships reduce accountability. Private entities usually restrict public access to information and do not have the same level of openness as the public sector. Long-term contracts, in particular, typically reduce accountability and transparency because the

nature of the contract may require projecting needs far into the future, creating terms that are incomplete or riddled with uncertainty.

In response to question 17, "what are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them," we believe that Federally mandated EHS research is the highest impact opportunity for advancing life science research.

In closing, we remind the Administration of its duty to ensure protection for human health and the environment. We urge you to move beyond encouraging EHS research to requiring it. And we ask that you place a moratorium on commercialization of emerging biotechnologies, including nanotechnology, synthetic biology, genetic engineering and geoengineering, until advanced risk assessment tools have been identified and an effective regulatory system is in place.

Sincerely,

Wenonah Hauter
Executive Director

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American Society for Biochemistry and Molecular Biology, Office of Public Affairs

BENJAMIN W. CORB
Director

JULIE M. MCCLURE, PH.D.
Science Fellow

The American Society of Biochemistry and Molecular Biology is a nonprofit organization representing over 12,000 research scientists. ASBMB is strongly supportive of President Obama and the Office of Science and Technology Policy in pursuing the advancements in biological research to address our national goals and concerns. ASBMB agrees that maintaining America's global leadership status in innovation requires continued support of basic research through strong, sustained federal funding. Basic research has always been the lifeblood of American innovation in science and technology. Countless examples of "game-changing" innovations, such as sequencing the human genome, statin drugs, modern HIV treatments, targeted cancer therapies, organ transplantation/anti-rejection drugs, and the recent introduction of anti-clotting drugs such as dabigatran and eptifibatide have their foundations in basic research. ASBMB enthusiastically agrees with the administration's efforts to better utilize the power of biological research. In addition, we argue that long-term success requires ongoing emphasis on the innovation pipeline through basic research, even as we develop recent discoveries to meet the "Grand Challenges."

In the following section we will present our responses, to questions 1, 2, 3, 4, 5, 6, 9, 10, and 12. As ASBMB is primarily composed of basic research scientists, we will address those questions related to our collective expertise. Each response addresses the specific issues within the question with the overarching goal of sustained federal funding for investigator-initiated basic research.

Responses to Questions for the Bioeconomy Blueprint

(1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations and other stakeholders to achieve this goal.

RESPONSE: Research conducted by ASBMB members encompasses all of the areas mentioned; i.e. health, energy, the environment, and agriculture. ASBMB represents significant non partisan scientific expertise, and we offer ASBMB as a resource for information and advice.

A. Providing for the health care of an aging population: In the United States in the year 2000, nearly one in every eight citizens was 65 years of age or older. By 2030, the U.S. Administration on Aging projects that number to increase to 72.1 million – or one in every five Americans. An aging population will increase the percentage of the U.S. population suffering

from Alzheimer's disease, cancers, obesity, diabetes, with the threat of overwhelming the health-care system. New treatments are needed for these afflictions

   a. **Specific recommendations:** A clear track record of successes demonstrates that new treatments will spring from continued support of basic research. ASBMB recommends strong, uninterrupted funding to the National Institutes of Health for investigator-initiated basic research on disease mechanisms related to Alzheimer's disease and cancers.

B. The obesity epidemic**:** Obesity in the U.S. requires approaches including public health/nutrition education, as well as scientific research
   a. **Specific recommendations:** Increase public health messages for preventative medicine through better nutrition; provide healthful food to low-income children to replace less-expensive fatty and salty foods that contribute to poor health.
   b. **Specific recommendations:** Ensure strong, uninterrupted funding to the National Institutes of Health for investigator-initiated basic research leading to a scientific understanding of the cellular and molecular mechanisms of obesity development, which could lead to more effective treatments for Type II diabetes.

C. Diagnostics and preventative medicine: Prevention and early detection of diseases not only increase the probability of successful treatment but can also drastically decrease the overall health-care cost associated with many preventable or treatable conditions.
   a. **Specific recommendations:** Continue to support interdisciplinary research at the nexus of physics, chemistry, biology, and computational science and engineering. Encourage the development of personalized medicine to include genomic and proteomic database development for individual patients to inform life style decisions and choices throughout the life cycle. Continue to invest in non-invasive methods for detection and treatment of disease, including advanced imaging methodologies.

D. Agriculture: ASBMB's position is that genetically modified food will be an important part of a broad strategy to feed an expanding global population. Biases and concerns about GM foods are impeding progress.
   a. **Specific recommendations:** Partner with organizations like ASBMB to design fact-based public information strategies and educate the U.S. public about the need for further research on the use of GM foods.

E. Energy: ASBMB agrees that the development of clean and sustainable energy is a critical issue for the U.S. Research in biochemistry and molecular biology has led to the development of fuel sources by harnessing solar energy from genetically modified bacteria or by converting plant material through biochemical modifications.
   a. **Specific recommendation**: Further develop existing programs that focus on alternative-fuel production. Expand the current tax-

benefit guidelines for production of renewable biofuels to include newer forms of biodiesels, such as cellulosic and algae-based fuels.

(2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies and infrastructure to provide the foundation for the bioeconomy?

RESPONSE:
ASBMB notes that the instability of federal funding for scientific research has placed our research enterprise and innovation engine at great risk. Other countries such as China and Singapore are investing very heavily in basic science and are successfully recruiting U.S. faculty and research trainees.

ASBMB recognizes and enthusiastically supports developing technologies that already have been shown to have game-changing potential. However, ASBMB argues in the strongest possible terms that the U.S. must not use the term "high-impact research" to justify supporting and developing only today's knowledge. We re-emphasize the critical importance of a constant and vigorous supply of new discoveries to feed the innovation pipeline, lest the pipeline dry up when current knowledge has been developed. In addition to feeding the pipeline, there are significant economic advantages. Entire industries have been built on unanticipated game-changing discoveries founded on investigator-initiated research, including recombinant DNA technologies and RNA interference.

Specific recommendations:

a) History has shown that many high-impact discoveries grow from asking fundamental questions; therefore, ASBMB recommends placing high priority on basic, investigator-initiated research for federal funding.
b) Further, in order to take these basic discoveries and apply them to health and technology issues, ASBMB also recommends a balanced federal investment in translational and clinical research that leverages partnerships with industry and pharmaceutical companies.
c) Invest in training a highly skilled workforce by funding graduate school science education and by enhancing K-12 programs in science and mathematics.

(3) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

SEE RESPONSE BELOW

(4) The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

RESPONSE TO QUESTIONS 3&4: Included among the greatest accomplishments of modern biology are the tremendous advances that have been made in applying high throughput technologies for experimental analysis. However these accomplishments present significant challenges because of the vast amounts of data that are generated. New computer algorithms for analyzing large datasets, as well as highly trained individuals who can develop and apply the analysis methods, are urgently needed.

Specific recommendations: Funds should be directed toward the development of more efficient computer algorithms that can analyze, model and simulate large datasets while being usable by laboratory investigators. Programs seeking to unite the work of highly skilled computational researchers with that of biological researchers will be beneficial. ASBMB also recommends increased educational programs that provide students/researchers with a strong understanding of both computational and biological approaches. In addition to computational efforts, funding should also be focused toward large-scale experimental efforts, such as validated and publically available RNAi libraries, mouse knockouts and proteomic probes, that can aid in the prediction of protein functions while computational methods are being optimized.

(5) What are the barriers preventing biological research discoveries from moving from the lab to the commercial markets?

RESPONSE: One of the greatest obstacles facing researchers interested in transitioning their discoveries from the lab to the commercial market is university-mandated technology-transfer policies. Unfortunately this problem is further complicated by the fact that these policies are unique to each university.

Specific recommendation: ASBMB suggests OSTP commission a study across universities to identify the best practices that will grant investigators the greatest ease in commercializing their discoveries.

RESPONSE: Over-regulation is another problem that stunts research in general, preventing biological research discoveries from moving from the lab to commercial markets. Animal-use regulations and conflict-of-interest regulations are important; however, these regulations take on a life of their own as university administrators build their own regulations on top of federal regulations. This problem seems to stem from a fear among universities of penalties for non adherence but has the result of introducing undue regulatory burdens.

Specific recommendation: Convene a forum for federal representatives, university faculty and administrators to identify best practices for regulatory

policies that protect animals and avoid conflicts of interest without duplication and the constant addition of unjustified standards.

(6) What specific changes to the SBIR / STTR programs would help accelerate commercialization of federally-funded bioeconomy-related research?

RESPONSE: ASBMB supports the SBIR/STTR concept; however, these programs must be optimized to ensure the highest quality to meet pressing needs.

Specific recommendation: Review the eligibility criteria for SBIR/STTR grants, which are currently overly restrictive and exclude many investigators at universities or research institutions.

Specific recommendation: ASBMB recommends that the quality of the SBIR/STTR programs would be enhanced if the scientific community played a greater role in identifying projects that receive consideration for funding.

(9) What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

RESPONSE: The preparation of scientists and engineers for private-sector bioeconomy jobs must begin at a stage that far precedes professional training programs. Unlike in Asia and other parts of the world, accomplishments in mathematics, science, and engineering in U.S. K-12 (and some university) students are often viewed with significantly lower regard than accomplishments in athletics, for example. The national ethos needs re-aligning so that young students see that careers in the sciences are valued and valuable.

Graduate students are the primary workforce of the academic research enterprise and are a vital component for its progression. While many graduate students remain in laboratory-based research careers, increasing numbers of students are moving to careers in private industry, education and even science-related, non laboratory professions. Part of the efflux of graduate students from research professions is a result of the funding insecurity faced by many investigators. A stable funding environment would make research professions more attractive and help retain graduate students in the research enterprise.

Specific recommendation: Maintain and strengthen the pipeline of scientists and engineers by funding graduate school training programs.

Specific recommendation: Convene groups of university faculty and industry leaders to discuss respective needs for preparing university academicians and private sector scientists. Recommendations could be used to consider enhancements to Ph.D. curricula or the further development of degree programs that combine biological research with other skills sets, such as business, law, education, and public policy.

(10) What roles should community colleges play in training future bioeconomy scientists and engineers?

RESPONSE: While the research enterprise is dependent on a skilled and knowledgeable workforce, the American bioeconomy would greatly benefit from a scientifically literate general population.

Community colleges are the first and often only exposure many Americans have to higher education and should be viewed as a critical component to increasing the scientific literacy of our society. Community colleges also serve as an opportunity for high school graduates to reinforce their math and science skills, ensuring they are prepared for the rigors of a university education. ASBMB acknowledges that community college professors must have a high level of scientific knowledge in order to adequately instruct their students on the importance and relevance of science.

Specific recommendation: ASBMB supports federal incentives to attract highly trained individuals to teach at community colleges to expose students to the highest level of scientific information.

Specific recommendation: Community colleges are well positioned to offer degree programs in laboratory management to supplement the more highly skilled Ph.D.-level scientific workforce. ASBMB encourages the federal government to convene discussions among industry/private sector scientists, university faculty, and community college faculty to generate recommendations relevant to developing a career track for laboratory managers that would represent a stable workforce to support the bioeconomy.

(12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students and postdocs?

Specific recommendation: Rapid progress can be achieved by learning from, and applying successful existing models, such as the Massachusetts Institute of Technology, where many faculty are entrepreneurs, where the university administration supports faculty interests in entrepreneurship, and where a local bioeconomy ecosystem has developed around the university. The federal government should develop programs permitting academia and industry to work together more closely, meaning that intellectual property issues must be resolved so that both industry and academia are rewarded.

Specific recommendation: To encourage entrepreneurship, ASBMB is supportive of undergraduate and graduate programs that combine research experience and business training and believes the federal government should invest in programs that introduce concepts in entrepreneurship without diluting the intensity and focus of the scientific training that forms the core of U.S. strengths in science and engineering.

Response to Building a 21st Century Bioeconomy

From: Critical Path Institute
Tucson, Arizona 85718

1. Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal?

Grand Challenges: The "Human disease-ome"

The National Institutes of Health (NIH) has invested billions of dollars in sequencing and studying the genome and determining how genes influence the many human biologic pathways. However, linkages between genes and human disease have been relegated to scientifically weak association studies whose results are often misleading and cannot be replicated. Lack of reproducibility of molecular targets for potential therapeutic interventions has been identified as a serious impediment that slows or prevents translation of the science to marketed products. The result is, in spite of all of this research, the number of new drugs approved by the FDA has remained at about 20-35 per year for over two decades. The major problem in clinical research is that the wealth of genetic disease data cannot be systematically linked to the patients and their diseases. Our scientists have sequenced the human genome, but we don't have the "disease-ome" that describes the natural history of diseases in ways that can be linked to genes, biomarkers and other mechanistic biologic probes. In the many subsets of the population, we need to be able to track the natural history of diseases characterized by the genes and thousands of biomarkers that have been discovered. We need efficient ways to obtain longitudinal data directly from patients using valid instruments, i.e. patient-reported outcome (PRO) measures. Once these data are available, we will be able to address the need for a more modern system to diagnose diseases and to replace the recently updated but completely outmoded ICD10 codes, a priority recently identified in a report from the National Academy of Sciences.

Another of the limiting factors holding back medical advances is our reliance on an outdated and dysfunctional clinical trial system. The Institute of Medicine's recent report found that the National Cancer Institute's clinical trials system to be unacceptably inefficient and several other IOM reports have repeatedly called for transformation of the clinical trial infrastructure.

We suggest a grand challenge to develop the human disease-ome. The first step would be to convene the clinical scientists and professional societies in order to define the common data elements needed to characterize and track the clinical course of patients with each known disease. This is feasible and the process has been begun by the FDA-designated international standards-setting organization, i.e. the Clinical Data Standards Interchange Consortium (CDISC).

CDISC partnered with the Critical Path Institute (C-Path) to form a public-private partnership that includes over 1000 scientists from 15 pharmaceutical companies, patient advocacy groups, FDA and NIH. These collaborators recently released to the public the final data standards for Alzheimer's disease clinical research and they are making progress on four other diseases. Once the common data elements were established, the companies pooled the control arm for 20 trials and placed data for over 5600 non-identifiable patients into the public domain. Using these data, quantitative disease progression models have been developed and are now available to support simulation of new clinical trials.

At the encouragement of the FDA, CDISC and C-Path have launched a new joint venture, the Coalition For Advancement of Standards and Therapies (CFAST). CFAST is prepared to begin work on 55 diseases identified as high priority by the FDA and they are in the process of gaining commitments from the biopharmaceutical industry to pool clinical trial data as was done for Alzheimer's. The goal of the grand challenge would be to have similar tools available for almost all diseases, beginning with the 55 identified by the FDA, but supplemented to include rare diseases, diseases of unmet medical need or special populations and diseases affecting global health.

The disease-ome could be started with data from clinical trials and then supplemented with data captured electronically from electronic health records. This would make the disease models "living," up-to-date descriptions of the spectrum of manifestations of diseases.

The ability to capture live data at the point of healthcare delivery will require the use of mobile device communications platforms with data privacy and confidentiality at a level now held only by the military.

2. Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

The first priority has to be the establishment of common data elements and links to the electronic health records so that we can truly have a "learning health care system."

3. What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research?

The major challenge in healthcare today is addressing our inability to link symptoms, behavior, and interventions to the outcomes of specific patients. Most systems today provide an average or mean response and almost all are plagued by late or incomplete data. For example, one third of prescriptions recorded in an electronic health record (HER) are never picked up at the

pharmacy, one third are not taken as directed and 40% of people are taking medicines that are not in the EHR because they were obtained from an unknown source (internet, another healthcare system or a relative). We must be able to track these and other metrics of care in a timely, unobtrusive and inexpensive manner if we are to ever have the ability to assess and improve healthcare.

4. The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

The limiting factor is the lack of phenotypic data on the patients. Efforts described above would set the foundation for obtaining such data.

5. What are the barriers preventing biological research discoveries from moving from the lab to commercial markets?

A major impediment is the hodge-podge of university tech transfer systems that delay publication of new findings and interfere with commercialization by unrealistic demands for licenses and royalties. The nation needs to require that all data developed with public funds be posted and made public. IP should be declared and revenues to inventors determined after the technology has demonstrated value.
A second impediment is the antiquated and overly intrusive IRB system. Clinical research protocols should have an IRB of record and all Universities and others executing the protocol should be required to accept the approval of the first IRB's approval. Patients should be informed that additional research on their biological samples may be performed if approved by the IRB in the future and that their identity will be protected. Additionally, data from each trial should be made available to all participants from that trial as a way to enhance transparency and disseminate knowledge.

6. What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?

Small businesses that are developing products for FDA approval should be better informed on the many precompetitive, critical path public-private partnerships established by Critical Path Institute and the FDA. These companies need to be better informed on how and when to utilize the newly developed tools for drug development, i.e. qualified biomarkers, PRO instruments and quantitative disease models.

7. What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

De-identified patient level data from all NIH-sponsored clinical trials should be made public 60 days from completion of any trial so that it can be used by other scientists.

8. What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

All restrictions on the level of venture funding should be removed from SBIR awardees so that the very best technologies can be supported.

9. The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Doctoral students should be encouraged to work in the commercial sector for a period of time to gain experience in team work and the corporate world of timelines, deliverables and accountability. Corporations should be given incentives to offer more fellowships and internships.

10. What roles should community colleges play in training the bioeconomy workforce of the future?

Community colleges can train students to better perform important scientific roles such as biospecimen handling and preparation using Standard Operating Procedures to gain greater reliability of biomarker assays. Community colleges are a rich source of talented minority students. To produce the diverse workforce required for optimal health care research and delivery, these students should be encouraged through special programs and scholarships.

11. What role should the private sector play in training future bioeconomy scientists and engineers?

Encourage internships at companies that partner with universities

12. What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

Encourage and reward faculty and students when they participate in startup companies.

13. What specific regulations are unnecessarily slowing or preventing bioinnovation?

Not responding

14. What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system?

Food and Drug Administration: As discussed above, the FDA is responsible for approving most of the scientific advances that result from the nation's $100 billion annual investment in biopharmaceutical R&D. Since the passage of the Prescription Drug User Fee Act, the industry has offered to pay more and more money and in return has expected more and more certainty for the development process by asking the FDA to tell companies in advance what type of evidence will be required for approval of their products. This assumes that the FDA will have the expertise to provide reliable advice when in fact that level of expertise is often missing and the advice given is inconsistent, at best. In Europe this advice is provided by the best expert consultants available to the regulatory agencies and is perceived by the industry as superior to the advice provided by the Agency.

In 2004, the FDA recognized that the methods being used by the industry were outmoded and the Agency launched the Critical Path Initiative to create collaborations to identify, through consensus, the best methods to test new products. In 2007, part of the User Fee reauthorization (FDA Amendments Act, FDAAA) included a provision introduced by Congresswoman Gabrielle Giffords to create Critical Path Public Private Partnerships. The first and most successful of these has been the collaboration between the FDA and the Critical Path Institute (C-Path), a unique non-profit organization, based in Tucson, Arizona. C-Path was launched in 2005 by Governor Janet Napolitano with over $24 Million over 6 years in support from the Arizona community. While C-Path's current annual budget is only $8 million/year, it leverages this relatively small amount of funding from the FDA, the Arizona governments, community foundations and the Bill & Melinda Gates Foundation. Last year C-Path's 35 industry partners contributed and made public, data estimated at $350 million in value. C-Path has five drug development consortia in which over 800 industry scientists work closely with over 200 scientists from the FDA to identify more reliable, efficient and innovative methods for testing drugs. This is the most appropriate forum for reaching independent consensus on the most advanced testing methods. This process should yield the "independent" stamp of approval for innovative testing methods so that FDA reviewers can focus on their legislatively mandated role, i.e. determining whether a medical product has been found safe and effective. By directly influencing the sponsors' development plan, the FDA has placed itself in a position of perceived conflict of interest. How can the FDA's objectivity be assured when the FDA scientists are evaluating products that were developed according to their own recommendations? An independent process for certification of testing methods should be established by a neutral entity such as one of the critical path public private partnerships where all stakeholders can share precompetitive science, knowledge and expertise.

15. What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement?

The FDA should move the Office of *In Vitro* Diagnostics into the Center for Drug Evaluation and Review (CDER) so that there can be greater efficiency and expertise in the review of companion diagnostics and drug-diagnostic co-development.

Secondly, there should be no restrictions on who can serve as advisors to the FDA. All conflicts of interest for advisors should be disclosed publically. Federal employees such as those at the NIH should be designated as consultants to the FDA for early determination of what type of evidence should be obtained in support of product approval. Product developers should be encouraged to use methods that have been independently certified by a scientifically rigorous, consensus-driven process.

16. What are the highest impact opportunities for public-private partnerships related to the bioeconomy?

The critical path public private partnerships created under FDAAA, should be given greater financial support and greater staff support from the FDA (see conflict of interest statement at the end of this document).

17. What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them?

The greatest impediment to biomedical research is the lack of understanding of the pathogenesis of diseases. A greater focus on developing "read outs" for vulnerable pathways responsible for diseases would create opportunities for biopharmaceutical companies to develop effective interventions or preventions. As soon as NIH and French scientists identified HIV as a retrovirus, Burroughs Wellcome was able to develop AZT in 18 months. FDA scientists were involved directly and their review of the AZT NDA was completed in 6 weeks. The average development time for 9 HIV drugs was 3.3 years. No safety shortcuts were taken and all of these drugs are still in use today. The grand challenge described above can create the tools and the environment for replicating the HIV/AIDS successes. Government should require NIH and FDA scientists to work in precompetitive consortia and should share in funding the work. The SEMATECH experience with the semiconductor industry should serve as a prototype for how to support the Critical Path Public Private Partnerships.

Conflict of Interest Disclosure: Dr. Woosley is President of the Critical Path Institute, a recipient of a collaborative award from the FDA that funds a critical path public private partnership designed to reach consensus on improved testing methods and drug development tools. Dr. Woosley does not receive any personal income from any company that is developing or marketing a product that requires FDA approval and therefore has no personal conflict of

interest. Critical Path Institute does not receive funding for its core operations from companies that are developing or marketing a product that require FDA approval. The author acknowledges and hereby discloses that some of the statements and recommendations in this response to the RFI can constitute a conflict of interest. This conflict is mitigated by the fact that Critical Path Institute is a non-profit organization with a public health mission working in partnership with the FDA, industry and NIH to advance medical product development.

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BIO
BIOTECHNOLOGY
INDUSTRY ORGANIZATION

James C. Greenwood
President & CEO

December 6th, 2011

Mr. Mike Stebbins
Assistant Director, Biotechnology
Office of Science and Technology Policy
Executive Office of the President
725 17th Street Room 5228
Washington, DC 20502

Dear Assistant Director Stebbins:

Biotechnology companies are working every day to solve the greatest challenges facing our society — whether it's finding a cure for cancer, protecting against bio-terror threats, or creating renewable energy sources. Yet despite the urgent need for scientific breakthroughs in these areas, some current government policies are holding back the potential and promise of biotechnology.

Only by transforming the policy environment can we create a robust innovation economy that helps America compete globally by maintaining our position as world leader in biotechnology research and development. And only by investing in biotech today can we unlock the scientific potential that resides in the thousands of American biotech companies and unleash the promise of biotechnology into the breakthrough cures, treatments, enhanced agricultural products, vaccines to defend against bioterrorism and revolutionary biofuels that can transform society.

To this end, BIO began a process in 2010 of interviewing thought leaders within and outside of our industry for the purpose of envisioning game-changing strategies. We contracted with Dr. Elias Zerhouni, former Director of the National Institutes of Health, to conduct an analysis of the challenges we face and a more comprehensive survey of medical experts, academic researchers, and other life science leaders to suggest out-of-the-box, big ideas to significantly advance biotechnology's chances to succeed.

Over the past year, we worked with BIO Board members and staff to review these ideas, debate their merits, and offer alternative and additional approaches to develop a comprehensive national policy strategy.

The policy agenda detailed in the accompanying materials is the result of this rigorous policy development process. It reflects the input and suggestions gathered throughout this process from biotech CEOs, venture capitalists, current and former government officials, academic and medical researchers, patient advocates and other experts. Our recommendations reflect the big, bold and daring thinking required to create new models to encourage investment in innovation and to speed up the discovery of scientific breakthroughs. In short, this agenda will enable the biotechnology industry to fulfill its promise to help, heal, fuel, and feed the world.

We are pleased to share these recommendations with you and look forward to working with the White House to create a bioeconomy blueprint for the 21st Century.

Sincerely,

James C. Greenwood
President and CEO
Biotechnology Industry Organization

Cc: Greg Nelson, White House Office of Public Engagement
Mary Maxon, White House Office of Science and Technology Policy

Introduction

In the last century, technological know-how (human capital) and physical capital have replaced land, labor and natural resources as the primary drivers of economic growth. Governments that have 1) invested in scientific research and technology development and 2) created policies and institutions to encourage the growth of scientific understanding and technological innovation have profited from their investments. The overall economic well being of their citizens has improved, as has their longevity, infant mortality rates and quality of life.

Science-based technology development accelerates economic growth through its effects on industrial productivity. New technologies create new products and processes; stimulate the creation of new companies and even new industries; improve existing products and processes; and lower manufacturing costs. They also provide researchers with tools and techniques for discovering new products.

In the past two centuries the primary scientific drivers of technology development were physics and chemistry. Technological innovations rooted in these sciences were key components of the Industrial Revolution, Information Age and Green Revolution, all of which transformed the nature of our economies and structure of our societies.

Society now finds itself on the threshold of an era dubbed the Biology Century by a number of authors. In the 21st century, a deep and rich understanding of the fundamental mechanics of life processes and its molecular components will lay the foundation for the development of an array of biologically-based technologies. This set of technological tools, collectively known as biotechnology, will be the predominant force fueling innovation, stimulating economic development and transforming our lives.

Biotechnology is not a single technology but a collection of technologies. The common thread uniting these technologies is their foundation: they are based on living cells and biological molecules. They capitalize on the cell's capacity to reproduce itself; manufacture biological molecules precisely and repeatedly; degrade a variety of substances; and respond to environmental factors.

These are the very same capabilities humans have relied on for centuries and that have provided the foundation for many well-established industrial sectors, such as agricultural production, food processing, pharmaceutical manufacturing and waste treatment. The success of these industries has always hinged on effectively expropriating the biochemical processes of living organisms and shaping them to specific purposes. However, only recently have scientists uncovered the underlying mechanisms of the biological processes that industries relied upon. With today's biotechnologies, companies co-opt these same cellular capabilities knowingly and purposefully.

All of the biotechnologies in Table 1 can be used by the many industrial sectors listed in Table 2 to conduct basic and applied research; identify and solve problems; improve processes; and create new products and services. Consequently biotechnology, like all technologies developed in the last two centuries will stimulate economic growth by increasing industrial productivity.

This infiltration of biotechnology into many industrial sectors will serve as the foundation of the bioeconomy

Biotechnology capitalizes on unique cellular properties

The fundamental problems confronting people today are essentially the same problems they have faced for centuries - growing crops, treating diseases, getting energy - but the technological tools brought to bear on these problems have improved, especially during the last century. By using cells and biological molecules as the foundation of a technology, companies can develop products that capitalize on innate properties of life at that level: specificity, unity and reproducibility. These cellular properties impart unique characteristic to the products and processes developed through biotechnology that make them superior to earlier, comparable technologies that addressed the same problems.

Specificity, precision and predictability

Cells and molecules exhibit extraordinary specificity in their interactions, so the tools and techniques of biotechnology are quite precise and can be tailored to operate in known, predictable ways. As a result, the products of biotechnology should represent improvements over earlier, comparable technologies by being better targeted to solving specific problems; generating less severe side effects; and having fewer unintended consequences.

The specificity of cells and molecules also enables biotechnology-based detection/disgnostic techniques to identify substances that occur in minuscule amounts and, once identified, to measure them faster and with great accuracy.

Unity, flexibility and leveraging

Cells and molecules from very diverse organisms display remarkable similarity. Because all cells

1. work with essentially the same set of molecular building blocks;
2. use similar processes to manufacture and breakdown molecular building blocks; and
3. are able to read and implement the genetic instructions from virtually any other cell

the technologies based on cells and biomolecules allow great flexibility in developing products and solving problems. By working at the level of cells and molecules, all of nature's immense diversity becomes accessible, providing an unprecedented number of options for designing technological solutions to specific problems.

In addition, because of the unity of life, every research dollar spent on understanding the molecular basis of a cellular structure or process in one organism is capable of informing research and enhancing understanding of other organisms.

Reproduction, renewable resources and sustainability

Fossil fuels provide the energy and feedstock chemicals that currently drive the engines of economic growth. However, fossil fuels are non-renewable resources and a major contributor to greenhouse gas emissions. Processes based on fossil fuels generate unwanted by-products, some of which are hazardous pollutants. Continuing to base economic growth on fossil fuels is not sustainable because the resource base is nonrenewable and their use degrades the quality of

essential resources. Depletion and degradation or essential resources are inconsistent with the concept of sustainability – meeting society's current needs without sacrificing the ability of future generations to meet theirs. We must find a way to continue to grow the economy, but it must be done sustainably.

Because organisms contain molecules similar to those in petroleum, they can be used as sources of energy and material inputs in manufacturing processes. As a result, biotechnology could help replace fossil fuels with renewable resources, such as biomass. In addition to being renewable, these resources could lead to the creation of products and processes that generate less solid waste or pollution. If the products are composed of biological molecules, they will be biodegradable due to the unity of life principle just described.

Utilizing these remarkable and valuable biological properties of molecular specificity, unity of life, and the ability to reproduce will make investments in biotechnology key to the success of a bioeconomy.

The Grand Challenge for Agriculture: Doing More with Less

Throughout history, as human population growth increased the demand for food, animal feed, fuel and fiber, our agricultural production systems kept pace. In the mid-20th century, fears of a population-driven food crisis, primarily in the developing world, led to research and investment to intensify crop production there. From the 1960 – 2000, the Green Revolution increased food production in developing countries almost 200% from 800 million tons to 2.2 billion tons and global food production by 150% from 1.8 billion tons to 4.6 billion tons through the use of high yielding varieties that could resist herbicides and disease, irrigation, insecticides and fertilizers. Although some people, primarily in affluent societies, criticize the Green Revolution's environmental impacts, its methods: 1) saved one billion from famine; 2) halved the global percentage of undernourished people; 3) improved rural economies; and 4) protected approximately 2.2 – 3.8 billion acres of land from being cleared for crop production.

We still face the relentless challenge of feeding an ever-expanding population, which will reach 9 billion by 2050 and require at least a 70% increase in food, feed and fuel production. However, this time the challenge of increasing agricultural production is exacerbated by a confluence of interacting pressures in addition to population growth: increased competition for water and land; rising energy prices; a dietary shift from cereals to animal products; diminishing supplies of fossil fuels – the source of most agrochemicals; resources degraded from past activities; and the global effects of climate change.

The Green Revolution allowed us to produce more with more inputs, most of which are derived from nonrenewable resources. Our current challenge is to produce more with less and to do so in a sustainable fashion. Biotechnology provides a set of precise yet flexible tools for meeting that challenge.

Essentially all of the biotechnologies listed in Table 1 have applications that improve the quantity and quality of agricultural products. The tools that are useful in diagnosing human diseases, such as monoclonal antibodies, can also be used to identify plant and animal diseases. Metabolic engineering technology permits crop developers to improve the fatty acid profiles of the oilseed crops or shunt the plant's energy into producing more roots to enhance drought tolerance. Using insect cell culture we could greatly increase the use of precise biological control agents, such as baculoviruses, in pest control. The list of possibilities is virtually limitless. Identify a problem related to agricultural production, environmental protection, food safety and nutritional value, and one or more of the biotechnologies could be used to develop a solution.

To date, however, most attention has been focused on one biotechnological tool being used to improve agriculture – genetic engineering. Of all of the possible applications of genetic engineering to agriculture, only a few have been commercialized.

Accomplishments in Plant Biotechnology to Date

Biotech crops have already proven they can provide more with less, sustainably, by improving yields without clearing new land, while conserving soil, saving water, using less fossil fuel, both directly and indirectly, and enhancing biodiversity. In addition to environmental sustainability, two other dimensions of sustainability – economic and social – are also enhanced with biotech crops because improved farm incomes have preserved jobs in rural communities

In 2011, U.S. growers once again increased the number of acres they planted in biotech crops. According to the USDA's Economic Research Service, 94% of the soybeans and 88% of the corn grown in the U.S. were biotech varieties[1]. U.S. growers were not alone in choosing to increase their plantings of biotech crops. For the 15th straight year, global acreage of biotech crops saw a double digit percent increase in 2010, as more than 15 million farmers in 29 countries grew 365 million acres of biotech crops. Almost 50% of the biotech crop acres were grown by 14 million small farmers in 19 developing countries. Since being introduced in 1996, there has been an 87-fold increase in the global acreage of biotech crops, making them the most rapidly adopted agricultural innovation in history.[2] The rates of adoption in developing countries have usually been steeper than in industrialized countries. For example, biotech soybeans were first introduced in Argentina in 1996, and by 2001 they accounted for 90% of the soybeans grown there. Biotech cotton was first made available in only two provinces in China, Hebei and Shandong, and within three years 97% and 80% of the cotton crop grown were genetically engineered varieties.[3]

The take-home message is clear: where farmers have been allowed to choose biotech varieties, they have embraced the technology and stuck with it. Why? Economics.

[1] The primary biotech crops grown today in the U.S. are insect-resistant and herbicide tolerant varieties of soybean, cotton, corn and canola.
[2] By way of comparison, 10% of the corn acres in the U.S. were planted in hybrid corn five years after its introduction; within five years, over 50% of the soybean and cotton acres in the U.S. were biotech varieties.
[3] Neal Van Alfen, UC, Davis. 2004. Agricultural Biotechnology: How Big Is It Globally? In: *Agricultural Biotechnology: Finding Common International Goals*

Scores of studies in different countries have compared the economics of various biotech crops with their conventional counterparts. Not surprisingly, the results show that farmers, who are naturally very risk-averse, switch to biotech varieties because of the economic gains they provide. The magnitude of the benefit varies from study to study, crop to crop, and country to country, but the fundamental - and unsurprising - finding is that farmers, like other business owners, act in their own best economic interest. Why else would farmers continue to choose biotech crops over conventional varieties since biotech seeds typically cost more?

For example, a 2010 National Academy of Sciences (NAS) study found that U.S. farmers who grow biotech crops "are realizing substantial economic and environmental benefits…compared with conventional crops."[4] In their most recent study of global impacts, Graham Brookes and Peter Barfoot demonstrate substantial net economic benefits for farmers of $10.8 billion in 2009 and $64.7 billion from 1996 – 2009, in spite of higher seed costs.[5] Interestingly, the shares of the global farm income gains, both in 2009 and cumulatively (1996-2009), have been split equally between farmers in developing and developed countries, but the economic gains to individual farmers in developing countries exceed that for farmers in developed countries. Carpenter's 2010 meta-analysis of 49 peer-reviewed studies on the economic benefits of biotech versus conventional varieties in 12 countries also demonstrated that the gains for small farmers in developing countries exceed those for farmers in industrialized countries.[6]

The gains that matter most to growers are not global figures, but the improved incomes they experience in their own operations. Studies have shown farm-level gains ranging from a few dollars per acre to significantly more than $200/acre depending on the crop, year, current and past pest levels and control practices, country and region. The economic gains farmers enjoy result from higher yields, lower input costs, or both in some cases. The 2010 NAS study cites "lower production costs, fewer pest problems, reduced use of pesticides and better yields."

Since 1996, biotech traits have added a total of 83.5 million tons of soybeans and 130.5 million tons of corn to global production. The technology has also contributed an extra 10.5 million tons of cotton lint and 5.5 million tons of canola (Brookes and Barfoot, 2011). During the same timeframe, biotech crops have reduced pesticide spraying by 865 million pounds and lowered fuel use. The combination of higher yields and reduced production costs provided for the 1996 - 2009 cumulative farm income benefit of almost $65 billion; 57% ($36.6 billion) was due to yield gains, and $28.1 billion due to lower production costs. James[7] found approximately 25% of global farm-level income increase ($2.7 billion) in 2009 was due to reduced production costs (lower fuel costs, less pesticides used, lower labor costs), and the remainder to yield gains for biotech varieties: 9 million tons of soybeans, 29 million tons of maize, 2 million tons of cotton lint and .67 million tons of canola.

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[4] National Research Council. 2010. *The Impact of Genetically Engineered Crops on Farm Sustainability in the United States.* http://www.nap.edu

[5] Brookes, G. and P. Barfoot. 2011. GM crops: global socioeconomic and environmental impacts 1996-2009. PG Economics. United Kingdom. PG Economics has published a series of similar studies. www.pgeconomics.co.uk

[6] Carpenter, J. 2010. www.guardian.co.uk/commentisfree/cif-green/2010/apr/21/gm-crops-benefit-farmers

[7] James, C. 2010 Global status of commercialised biotech/GM crops: 2010, ISAAA brief No 42. www.isaaa.org

The follow-on environmental benefits of growing biotech crops are substantial and include preservation of biodiversity[8] and topsoil, while reducing greenhouse gas emissions, fuel use and water loss from soil. According to Brookes and Barfoot (2011):

• Without biotech crops, the 2009 production increases would have required clearing 31 million acres of land for crop production and, as a result, decrease biodiversity.

• Herbicide tolerant biotech crops have facilitated the adoption of no/reduced tillage production systems in many regions, which reduces soil erosion and improves soil moisture levels

• In 2009 alone, less fuel use and additional soil carbon storage from reduced tillage reduced greenhouse gas emissions by an amount equivalent to removing 17.7 billion kg of carbon dioxide from the atmosphere or removing 7.8 million cars from the road for one year.

The Potential for Agricultural Biotechnology to Do More with Less

The past achievements of biotech crops pale in comparison to what agricultural biotechnology could provide, especially in light of the necessity of doing more with less.

The "less" we have already experienced with the existing biotech crops – less fuel, land, pesticides, soil erosion – could be extended to many more crops, including orphan crops essential to subsistence agriculture in developing countries and, as such, key to their food security. For example, genes for the insect-resistance trait developed for corn and cotton, which come from a naturally occurring microbe found in soils worldwide, *Bacillus thuringiensis* or Bt, have been donated to African institutions for use in cowpea, a staple crop in West Africa.

In the U.S. these proven traits could be transferred into minor use or small acreage crops and significantly increase the incomes of famers. This crop diversification not only gives farmers more options but also has been proven to enhance the sustainability of agricultural systems. This flexibility is one of biotechnology's greatest untapped potentials: a genetic innovation developed for commodity crops can be used in any crop, because all plants know how to translate and use the genetic information.

The tools of biotechnology are also being used to develop new crops that use less of other essential resources: water and fertilizers. Drought tolerant corn varieties developed through biotechnology are awaiting approval in the U.S. and other countries, and drought tolerant genes have been incorporated into African corn varieties. A number of crops with the NUE trait (nitrogen utilization efficiency) are also in the pipeline.

"Less" means not only lower amounts of agricultural inputs, but also less severe environmental impacts. The pest control traits of current biotech varieties have had less severe environmental impacts than their predecessors, and therefore less of an impact on biodiversity. The Bt gene is toxic only to a handful of insects, and in order to exert its effect, the insect must eat the crop. As a result, insects that are not crop pests or are beneficial, such as bees and ladybird beetles, are not harmed. The herbicide tolerance traits added to biotech crops, have allowed farmers to switch to herbicides with fewer environmental and health impacts.

[8] Carpenter, J. 2011. Impacts of GM crops on biodiversity. *GM Crops:*2:1-17.

This same thinking could be applied to crops to control disease, such as those caused by fungi and virus. We have long had the technology to create many virus-resistant crop varieties, but the economics of product development, primarily the costs of regulatory approval, make it unlikely that these will be developed for any but the largest commodity crops.

Just as "less" means more than less inputs, the "more" provided by past and future advances in biotechnology encompasses more than just "more" product. More farm-level income, with its concomitant impacts on rural economic development, could be provided to many more farmers, including those growing small acreage crops in the U.S., if existing biotech traits were incorporated into additional crops, especially small acreage crops.

The "more" provided by biotechnology also entails more nutritious crops, thus enhancing agricultural biotechnology's contribution to public health. A few crop varieties, nutritionally-enhanced through biotechnology, have been commercialized in the U.S. and could help to address the obesity epidemic by shifting the proportion of various oils to healthier types. Similar work is being done with animal food products in which the levels of omega-3 fatty acids, which have many health benefits, in meat and milk are increased. However, much more could be done to improve the vitamin and mineral content, as well as local availability, of fruits, vegetables and other crops, both in the U.S. and globally. Some of these "biofortified" products are currently being field-tested in developing countries, and many more are under development by public sector research institutions. However a number of studies have shown that the high costs of regulatory approval makes ii essentially impossible to create these biotech crop varieties

We already have the know-how to develop the biotech varieties just described that would allow us to do "more with less." We have the necessary genes in hand, have developed the technology to provide them to various crops and, in many cases, have already produced the biotech variety. But having these much needed technologies is not sufficient. We also need government policies that will allow both the public and private sectors to develop these crops.

Realizing the Potential through Regulatory Reform

Agricultural biotechnology holds essentially unlimited potential for improving food and energy security, making food safer and more nutritious, enhancing the sustainability of both agricultural and energy production systems and sustaining rural economies. Unfortunately only a sliver of that promise has been turned into reality. Why? The U.S. regulatory system, which was originally structured to facilitate product development by verifying science-based predictions of product safety, is the greatest impediment to the development of safe, beneficial products. Irrespective of the intent of the U.S agencies in the 1980's (and their verbiage today), our regulatory system is neither risk-based, nor scientifically sound.

Agricultural biotechnology has a sterling safety record, which was anticipated in reports published by scientific bodies from around the world prior to the first field test and has been

reiterated often since then.[9] Scientific understanding of biology, food safety and agricultural ecosystems allowed them to predict that the environmental and food safety issues associated with these crops would be the same as those of conventional crops. In other words, the concerns focused solely on biotech crops, such as gene flow and the evolution of resistance to herbicides and Bt crops, are the very same concerns that apply to agriculture, in general.[10] Twenty-five years of testing and experience confirmed the predictions of the scientists, as there have been no documented adverse effects to human health or the environment from biotech crops.[11] None of the hypothetical problems that people raised well before the first crop was planted or eaten has come to pass after over 2 billion acres of biotech crops have been grown and an incalculable number of meals, consumed.

However, as evidence that ag biotech products pose minimal to no risk has accumulated over the last two decades, the degree of regulation, as measured by the amount of data that must be submitted to a U.S. regulatory agency in applications for product commercialization, has increased, not decreased. For example, the attached chart of the U.S. Environmental Protection Agency's data requirements clearly demonstrate the increase in the type and scope of information that must be submitted for registering a crop with a single gene encoding a Bt protein (Table 3). Similar increases in data requirements, accompanied by delays in decision-making, are found at the United States Department of Agriculture regulatory agency, as well.

This increase in data requirements has led to a staggering increase in the time and cost of getting a product through the regulatory approval process. [12] A September 2011 study of the six large ag biotech companies[13] involved in product development, conducted by Phillips McDougal in the United Kingdom, revealed the following trends related to ag biotech innovation:

- The cost of discovery, development and authorization of a new plant biotechnology trait introduced between 2008 and 2012 is US$136 million. Of that total, $35.1 million is spent on the costs of meeting regulatory requirements. [14]

- The time from the initiation of a discovery project to commercial launch is 13.1 years on average for all relevant crops. Regulatory science, registration and regulatory affairs

[9] A few of the scientific bodies that have issued scores of statements about the environmental and food safety of biotech varieties are: WHO, FAO, U.S. National Academy of Sciences, OECD, American Medical Association, American Dieticians Association, International Academies of Sciences, Ecological Society of America.

[10] As stated by Dr. Marc Van Montagu of Ghent University in *A Decade of EU-funded GMO Research*, "The current focus on assessing the environmental risks of GMOs in isolation from other agricultural practices defies logic."

[11] For example, a book published by the European Commission in December 2010, *A Decade of EU-funded GMO Research*, summarizes the results of 50 EU projects on the safety of biotech crops: there is "…no scientific evidence associating GMOs with higher risks for the environment or for food and feed safety than conventional plants and organisms."

[12] Those who developed the regulatory system in the 1980's estimated the maximum cost for obtaining regulatory approval of a genetically engineered crop with which they had no familiarity at $500,000. Today, approval for that very same crop, for which we now have decades of experience, is over $30 million.

[13] The September 2011 survey entitled, "The cost and time involved in the discovery, development and authorisation of a new plant biotechnology derived trait", focused on biotech traits in large scale commodity crops that had received cultivation approval in two countries and import approvals from at least five countries.

[14] It should be noted that this study was designed to exclude the costs and timelines for products with multiple events combined by breeding ("breeding stacks"). For breeding stacks, the total timelines are commonly, depending on the crop, 2-3 years longer than what is represented by this data.

> accounts for the longest phase in product development, estimated at 36.7 percent of total time involved. The time associated with registration and regulatory affairs is increasing from a mean of 3.7 years for an event introduced before 2002, to the current (2011) estimated 5.5 years.

A number of unfortunate trends result from the significant increase in costs of obtaining regulatory approval for a genetically engineered crop.[15] The richness of the 1980's-90's pipeline, which was filled with a wealth of different traits, in scores of crops, being developed by the public sector and companies of all sizes, evolved into one containing very few traits in 4-5 crops being developed by a handful of large companies.[16] According to Miller and Bradford,[17] "..innovation in ag biotech was on an exponentially increasing trend during the 1990s, which then abruptly leveled off around 1998 with a decrease in subsequent years." They attribute this precipitous decline in innovation to the increasing cost of regulatory approval for biotech crops that can be recovered only for high volume commodity crops, such as corn and soybeans.

Unfortunately, researchers attempting to develop biomass crops for a bio-based economy have noted a similar stultifying effect of biotech regulations on innovation in that field as well.[18]

The costs of that attrition of safe and beneficial products are many and diverse: consumers do not have access to safer, more nutritious fruits and vegetables; small and large farmers are not able to diversify and profit from value-added crops; and new energy sources and environmental benefits are lost to all.

The other losers are small companies and universities, one of the country's greatest sources of jobs and innovation. Both have been essentially excluded from the ag biotech revolution by a regulatory system in which the degree of regulation is unrelated to the degree of risk.

Recommendation: If the potential of biotechnology is to be realized, the regulatory system must be restructured based on the fundamental principle that the degree of regulation should be proportional to the degree of risk. This might involve excluding classes of crops/traits from regulatory oversight based on familiarity or on science-based prediction of level of risk. This could be achieved by regulatory changes, perhaps in conjunction with minimal legislative language that facilitates and guarantees changes are realized.

The large companies that are able to afford the costs of regulatory approval, irrespective of the system's lack of scientific validity, are now suffering from a different regulatory challenge: the vulnerability of the regulatory-decision making process to litigation and politicization. As a result, rampant regulatory uncertainty is now the norm. Companies no longer can predict how

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[15] Pew Initiative on Food and Biotechnology. *Emerging Challenges for Biotech Specialty Crops*. Workshop Proceedings. (2007).

[16] Graff, G.D., Zilberman, D. & Bennett, A.B. The contraction of agbiotech product quality innovation. *Nature Biotechnology* **27**, 702-704 (2009).

[17] Miller, J.K. & Bradford, K.J. Regulatory bottleneck for biotech specialty crops. *Nature Biotechnology* 28, 1012 – 1014 (2010)

[18] Strauss, S.H., et.al. Far-reaching deleterious impacts of regulation on research and environmental studies of recombinant-DNA modified perennial biofuel crops in the United States. *BioScience* 60, 729-741 (2010)

long regulatory approval will take, which data will be required, what the decision will be, and what the decision will be based upon. The only thing they can be certain of is that it will take 6-8 times longer to receive approval for a crop/trait that would have taken 140 days in 1997.

Recommendation: Regulatory decision-making must be made less susceptible to litigation and politicization so that the regulatory certainty and timeliness return. One way to achieve this is by making regulatory decision-making more immune to attacks based on NEPA and the Endangered Species Act. Successfully achieving this protection will likely involve changes to the agencies' authorizing statutes. Other changes that would improve predictability and timeliness are those that provide additional resources to BRS and making the agencies more accountable.

Table 1. The biotechnologies. Biotechnology is a collection of technologies, all of which utilize certain unique properties of cells and the molecules within them. This list includes only some of the biotechnologies and focuses on commercial applications and not the uses of biotechnology in basic research.

Technology Description	Current and Potential Applications
Monoclonal Antibody Technology Uses immune system cells that make proteins called antibodies. Antibodies bind to substances with extraordinary specificity.	Diagnose infectious diseases Treat autoimmune diseases Detect harmful microorganisms in food Locate and measure environmental pollutants Distinguish cancer cells from normal cells
Bioprocessing Technology Uses living cells, such as bacteria, yeast and mammalian cells, or their enzymes, to manufacture useful products, breakdown molecules or generate energy.	Cleanup toxic waste sites Produce energy from agricultural refuse Manufacture therapeutic compounds & vaccines Produce fermented foods and nutritional additives Manufacture industrial enzymes & feedstock chemicals
Cell Culture Technology Is the growing of cells in appropriate nutrients in laboratory containers or in bioreactors in manufacturing facilities.	Increase use of biocontrol in agriculture Replace animal-testing with cell testing Treat certain medical problems by replacing malfunctioning or injured cells with healthy cells Produce naturally-occurring plant therapeutics
Biosensor Technology Consists of a biological component, such as an enzyme, linked to a tiny transducer that produces an electrical or optical signal when the biological component binds to another molecule.	Measure blood glucose levels Monitor industrial processes in real time Provide physicians with instant test results Locate and measure environmental pollutants Measure the nutritional value & safety of food
Recombinant DNA Technology (Genetic Engineering) Uses molecular techniques to join, or recombine, DNA molecules from different sources.	Treat certain genetic diseases Improve food nutritional value Develop biodegradable plastics Provide new and improved vaccines Enhance biocontrol agents in agriculture Decrease allergenicity of certain foods Increase crop yields & decrease production costs

Microarray Technology Allows analysis of thousands of gene, proteins or other molecules simultaneously.	Detect genes useful in crop production and protection Tailor drug treatment to patient Assess potential toxicity of drug Identify stage of disease progression Find microbes for cleaning up pollution
Protein Engineering Technology Improves existing proteins, such as enzymes and antibodies, and creates proteins not found in nature.	Create novel enzymes Improve catalytic ability of enzymes Develop sustainable industrial processes Improve proteins responsible for bread rising
RNA Interference Technology Decreases the production of specific proteins by blocking the genes encoding them.	Slow food spoilage Control viral diseases Engineer metabolic pathways in crops Treat diseases such as asthma and certain cancers

Table 2. Examples of the industrial sectors affected by the biotechnologies. This summary is not intended to be comprehensive but only suggestive of the potential role biotechnology will play in these industries.

Human Health Care
Knowing the molecular basis of health and disease can lead to improved and novel methods for diagnosing, treating and preventing diseases. Biotechnology products already on the market include detection tests for many infectious organisms, certain cancers, hormone levels and genetic diseases; therapeutic compounds for rheumatic arthritis, diabetes, cystic fibrosis and other genetic diseases, multiple sclerosis, cardiovascular diseases and many cancers; and vaccines for hepatitis B, meningitis and whopping cough.

Agricultural Production
The agricultural production industry uses biotechnology to increase yields, decrease production costs, diagnose plant and animal disease, enhance pest resistance, improve the nutritional quality of animal feed, broaden the use of biological control agents and provide alternative uses for agricultural crops. Currently marketed products include insect and disease resistant crops, herbicide tolerant crops, healthier oilseed crops and crops that provide renewable sources of raw materials for soaps, detergents and cosmetics.

Food and Beverages
Food processing, brewing and wine-making have always relied on biotechnology to enhance the nutritional quality and processing characteristics of their starting materials – grains, fruits and vegetables - as well as improve the microorganisms that are essential to these industries. All fermented foods and beverages depend on the action of microorganisms, which also serve as the source of many food processing aids, preservatives, texturing agents, flavorings, and nutritional additives, such as amino acids and vitamins. In addition biotechnology-based diagnostic tests are improving food safety.

Enzyme Industry
The enzyme industry and its products are essential to the operations of many of the other industrial sectors, such as food processing, textiles and brewing. Microorganisms have been the essential manufacturing work force of this industry, and their impact will increase in the future as genetic engineering gives new manufacturing capabilities to standard production microorganisms and improves manufacturing process efficiency and production economics.

Forestry/Pulp and Paper
Biotechnology is being used to create trees that are resistant to diseases and insects and to improve the efficiency with which trees convert solar energy to wood production. Extensive research is being conducted on microbes and their enzymes for pre-treating and softening wood chips prior to pulping; removing pine pitch from pulp to improve the efficiency of paper-making; enzymatically bleaching pulp rather than using chlorine; and deinking recycled paper.

Textiles
Many textiles, such as cotton, wool and silk, are naturally-occurring, while others are derived from natural substances, such as wood pulp. Biotechnology should have an indirect impact on

the textiles industry by improving the source materials, as well as a direct impact. Enzymes are currently used in natural fiber preparation and value-added finishing of the final product, such as stonewashed denim genes. Leather manufacturers use enzymes to remove hair and fat from skins and to make leather pliable. Genetically engineered microbes have produced textile dyes, such as indigo, and the protein found in spider silk.

Chemical Manufacturing

Biotechnology can provide cleaner, more efficient ways of manufacturing chemicals than do current methods. Microbes have been used for decades to convert biological materials, such as corn, into feedstock chemicals. Public and private institutions are conducting research on increasing the use of plant biomass and microbial enzymes in chemical manufacturing, because both are likely to generate fewer toxic waste products.

Energy

Before fossil fuels can be used for energy production, sulfur must be removed, and biodesulfurization relies on microbes and their metabolic enzymes. Microbes have also been used to enhance oil recovery from in-ground crude oil formations for more than 30 years. In the future, as fossil fuels become depleted and oil prices increase, we will need to establish alternative energy sources, such as biomass-based fuels like the ethanol that is currently added to gasoline. Advances in biotechnology are making production of ethanol more attractive economically. Other potential areas of energy production include genetically engineered microbes to generate methane from agricultural or municipal wastes or photosynthetic microbes for hydrogen production. However, both will require a number of decades of research before they become economically viable.

Waste Treatment

Microbes have always been essential for degrading organic wastes, whether the waste is generated by humans or agricultural and industrial operations. As the human population increases, supplies of potable water decrease, and the standard of living of people in developing countries improves, we will need to apply biotechnology to improving the efficiency of natural microbial degradation processes. In addition to utilizing microbes to breakdown wastes, we are also turning to microbes to help us clean up soils and water that have become contaminated with environmental pollutants.

Table 3. Past, Current and Future PIP (Proposed 2011) Data Requirements: Registration Applications for Plant Incorporated Protectants[1] (X= required)

(Although not listed in this Table, it is worth noting that in the proposed data requirements rule, the requirements for Experimental Use Permits have increased substantially. The data requirements below now apply to an application for an EUP, with the exception of the following.

- Under human health, the 90-day oral toxicity test, the specific serum binding test, and the hypersensitivity data;
- For nontarget effects, Tier II, III and IV tests;
- For environmental fate, the field persistence data; and
- Product performance and resistance management data.

This is a very onerous list for what could be a very small-scale field testing program.)

Data Category	**Bt Potato 1995**	**Bt Corn 2008**	**2011 Proposal**
Product Characterization			
Biology of the plant			New Requirement
Identification of the event	X	X	X
Identification of the PIP components			Increase Scope
Spectrum of pesticidal activity		X	Increase Scope
Mode of action	X	X	X
Certification of limits		X	X
Characterization of inserted DNA	X	X	Increase Scope
Characterization of protein - Efficacy		X	X
Characterization of protein – Expression levels	X	X	X
Physiochemical characterization of proteins	X	X	Increase Scope[2]
Demonstration of protein equivalency	X	X	X
Human Health			
Acute oral toxicity - Mouse	X	X	X
Allergenicity - Bioinformatics database analysis		X	Increase Scope
Allergenicity – Stability to heat, SGF, SIF		X	X

[1] Both of the crops have a single gene encoding a protein from a strain of *Bacillus thuringiensis.*

[2] Increase in scope is due to possible increase in number and type of proteins doe which data must be submitted (e.g., fusion proteins produced via insertions that inadvertently create new open reading frames), not to providing data on more physiochemical properties of the PIP)

Serum binding tests			New Conditional Requirement
Toxins – Protein database analysis		X	X
Non-protein toxicity			New Conditional Requirement
90-day oral toxicity			New Conditional Requirement
Hypersensitivity incidents			New Requirement[3]
Synergistic effects from multiple PIPs		X	X
Environmental – Non Target Organisms			
Soil microbial community acute toxicity			New Requirement
Broiler feeding study –transgenic grain		X	New
Avian oral toxicity – Quail/duck – purified protein	X	X	Increase Scope
Wild mammal – Oral toxicity – purified protein			New Conditional Requirement
Freshwater fish – Toxicity – purified protein		X	Increase Scope
Freshwater invertebrate - Toxicity		X	Increase Scope
Estuarine and marine animal		X	Increase Scope
Honeybee toxicity – Larva and adult	X	X	X
Arthropod toxicity – Ladybird beetle, lacewings	X	X	May Increase Scope
Arthropod – Minute pirate bug		X	X
Parasitic wasp	X	X	X
Non-arthropod invertebrate - earthworm		X	X
Tritrophic testing of selected beneficial insects			New Conditional Requirement
Tier II-IV testing – plant tissue testing; semi-field studies; field studies			New Requirement
Environmental – Environmental Fate			
Plant Studies			New Requirement
Impacts gene flow- sexually compatible plants			New Requirement
Potential weediness			New Requirement
Potential horizontal gene transfer			New Requirement
Field persistence			New Requirement
Soil degradation rate	X	X	Increase Scope

[3] Previously associated with adverse effects reporting (ex post facto). Now seems to be requirement in application submitted for the registration

Resistance Management Data Requirements			
Target organism biology and ecology			New Requirement
Target organism susceptibility		X	Increase Scope
Simulation models		X	X
Potential for cross resistance		X	X
Resistance monitoring plan		X	X
Remedial action plan		X	X
Compliance assurance/grower education		X	X
Conditions of Registration			
Annual Report on CAP		X	X
Annual Report on Grower Education		X	X
Annual Report on IRM Monitoring		X	X
Annual Sales Report		X	X
Other			
Analytical detection method		X	X
Public interest document		X	X

The Grand Challenge for Industrial Biotechnology:
Creating a Biobased Economy

Vision: The vision of the industrial biotechnology sector is the development of a thriving *"biobased economy"* in which the U.S. is no longer dependent on fossil fuels for energy and industrial raw materials, but instead derives much of its fuels, chemicals and materials from renewable agricultural feedstocks converted to higher value products by industrial enzymes and microorganisms or other processes. This vibrant biobased economy would revitalize rural and "rust belt" communities through the creation of high quality *jobs in value-added agriculture and clean manufacturing* of *sustainable domestically produced products*; strengthen the nation's *balance of trade* through exports from increased domestic manufacturing; enhance the country's *energy security* through reduced dependence on imported oil; and improve the nation's *health and environment* through cleaner burning fuels and more efficient manufacturing, which in turn would reduce emissions of greenhouse gases and other pollutants. The biobased economy would be a vital component of a broader "Bioeconomy" based on the innovation and commercial activity of the whole biotechnology industry.

Challenge: Today's fossil fuel-based economy is the product of over a century of private and public investment in fossil fuels. Industrial biotechnology offers a set of tools **(see Appendix A)** which can be used to develop the *fundamental value chains* of a biobased economy; but industrial biotechnologies must compete with mature and entrenched fossil incumbents and the accompanying infrastructure developed over the last century. Innovative industrial biotechnology companies must also have enough capital to vault over the *"valley of death"* that separates emerging technology companies from those that have successfully commercialized biotechnology innovations. One of the largest and most acute hurdles facing the biotechnology sector is the absence of private *financing* for the construction of first-of-a-kind and large-scale commercial *biorefineries.* Another significant hurdle is that a national infrastructure for the production, collection and processing of next generation feedstocks – such as cellulosic crop residues, dedicated energy crops and algae biomass – is lacking. Increased public investment in industrial biotechnology *research and development, and demonstration manufacturing facilities* is also needed to fund future waves of innovation that would proceed in parallel with market development and commercialization efforts. Specific challenges facing the industrial biotechnology sector follow.

R&D Funding. Federal agencies have provided solid funding to industrial biotechnology research, which has led to important innovations and ushered many technologies to the cusp of large scale commercialization. This is particularly true for biofuels, but there are still areas of industrial biotechnology research and development in need of similar attention – particularly for the development of renewable chemical platforms, which are the building blocks for industrial biotechnology. As commercialization proceeds, continued investment in innovation and process improvements will be needed to enhance the economic viability of projects and to continue to expand the industrial biotechnology product portfolio. Public-private research collaborations will continue to be needed to keep the U.S. competitive and maintain leadership in this space. Specific areas in need of ongoing research include synthetic biology, marine biotechnology, industrial biocatalysis (enzymes), feedstock improvement and processing, and development of new renewable chemicals, biobased products, and biofuels.

Specifically prominent among emerging technologies is "synthetic biology," **(see Appendix B)** which aims to apply standardized engineering techniques to biology, thereby creating organisms or biological systems with novel or specialized functions to address countless needs. This highly promising platform merits strong federal investment. The Administration should also strongly consider a dedicated program of research and development to produce a robust, affordable and sustainable supply of industrial building block sugars for conversion to fuels and chemicals.

Financing the construction of first-of-a-kind commercial biorefineries. A new generation of advanced biofuel and renewable chemical products and technologies, such as cellulosic ethanol, drop-in biofuels, and a host of promising renewable chemical intermediates **(see Appendix C, D),** has emerged from the laboratory and is ready for commercial deployment. But, because of the economic downturn, private financing for the construction of first-of-a-kind commercial-scale biorefineries is nearly non-existent. Commercial banks are reluctant to provide financing because they view these technologies as unproven at scale and high investment risk. With the downturn in the economy, venture capital investment has also diminished significantly. A growing list of industrial biotech innovators has exhausted operating capital and is in immediate need of assistance.

Establishing next generation feedstock supply chains. Achieving large commercial volumes of biofuels and renewable chemicals will require a robust and diverse renewable biomass feedstock supply with an emphasis on high-yielding, sustainable biomass sources such as purpose-grown energy crops, including algae. Commercial quantities of these feedstocks do not yet exist. A pathway to widespread adoption of purpose-grown energy crops is needed, including enduring programs to assist farmers in establishing such crops, equipment and infrastructure for collecting, storing and delivering the biomass, and processing technology and infrastructure.

Workforce training. A 2009 report on the "U.S. Economic Impact of Advanced Biofuels Production: Perspectives to 2030" (attached as **Appendix E**) found that advanced biofuel production under the federal Renewable Fuel Standard (RFS) is expected to create over 400,000 direct jobs in the United States by 2030. There are already hundreds of biofuels projects underway throughout the country to meet these requirements, including over 50 existing and planned cellulosic biofuel development projects. Renewable chemicals projects are expected to create tens of thousands of additional high quality jobs over the next decade (see **Appendix F, G**).

These projects are mostly in rural areas and all demand significant manpower in research and development, construction, sales, management, feedstock growth, harvesting, transportation, engineering, distribution, etc. Workforce training in all of these areas will be critical to achieving these targets (see **Appendix H**). In particular, there will be a rapidly growing need for chemical engineers trained to work with biological systems – skills that are already in short supply even at this early stage of deployment.

Regulatory support. Current environmental regulations are geared toward clean-up of end of pipe pollution. Such standards do not reflect the unique properties of industrial biotechnology to prevent pollution through cleaner, more efficient manufacturing processes. Revised regulatory approaches are needed to encourage the adoption of biotechnology processes that can prevent pollution before it ever occurs and can remediate existing pollution. Industrial biotechnology (green chemistry) inherently provides substantial gains in manufacturing of renewable chemicals and biobased products by reducing pollution and waste, decreasing the use of raw materials and water, and reducing the number of process steps.

For example, many proposed federal and state-based carbon regulations fail to adequately account for greenhouse gas emissions savings that can be generated by industrial biotechnology. Combustion of biofuels and other biogenic energy sources recycles CO_2 emissions through renewable biomass feedstocks. If sustainably sourced, such combustion does not result in lasting increases in CO_2 concentrations in the atmosphere. Other uses of biogenic carbon, such as renewable chemicals and bioplastics, may even sequester CO_2, reducing atmospheric GHG concentrations (see **Appendix I, J, K**). Life-cycle based methodologies should start from the

premise that all renewable biomass receive full credit for recycling of carbon. Attached please find BIO's comments to U.S. EPA and the California Air Resources Board (CARB) on proper accounting of biogenic carbon (**Appendix L, M, N, O**).

BIO also encourages OSTP to work with industry to ensure that regulation of algae-based fuels and renewable chemicals production is well coordinated among federal agencies and does not impede the development and deployment of this promising emerging technology.

Market access barriers. Biofuels face several barriers to increased market adoption, including ethanol blending limits, regulations and standards that restrict eligible fuel molecules or production pathways, and inadequate biofuel distribution infrastructure. In the case of new "drop-in" biofuel molecules such as biobutanol and renewable hydrocarbons, there are multiple statutory and regulatory barriers to the introduction of these promising new biofuels. A brief presentation summarizing these barriers is attached as **Appendix P**. For biobased products, existing programs to expand market adoption and consumer awareness, such as the USDA BioPreferred Program™, have been very slow to take shape, hindering the growth of these technologies. A short overview presentation illustrating USDA's BioPreferred Program is attached as **Appendix Q**.

Awareness and public opinion. A fundamental challenge for the industrial biotechnology sector is increasing public awareness and support for industrial biotechnology processes and products. Broad support has been established for advanced biofuels, but recent criticism of first generation biofuels (e.g. food vs. fuel; indirect land use change) has negatively impacted the confidence of policymakers, investors, and the broader public in biofuels generally. Awareness of renewable chemicals among policy makers and the public significantly lags biofuels, complicating the case for policy support.

Despite broad support for advanced biofuels, renewable chemicals, and biobased products, federal policies for these technologies have not fully overcome the full set of challenges facing the sector. For example, the impact of biorefinery loan guarantee programs has been limited by overly restrictive implementation; renewable energy tax incentives for other renewable energy technologies have become more generous steering investment to those sectors; and threatened cuts to farm bill energy programs have added to policy and project uncertainty. A new commitment to a biobased economy is needed in Congress and within the Administration to achieve President Obama's goals of economic prosperity, energy security, technology leadership, and environmental health.

Solutions: Strong, sustained, stable federal policy support is critical to overcoming the challenges facing the industrial biotechnology sector to create a biobased economy. BIO's 2011 Industrial and Environmental Section Policy Priorities identify the leading near-term threats and opportunities in federal industrial biotechnology policy. Strong Administration support for these priorities is needed to ensure continued development of the industrial biotechnology sector:

BIO Industrial and Environmental Section
2011 Policy Priorities

Funding/Eligibility - Maintain funding for biomass and biorefinery programs at USDA and DOE, and expand eligibility to renewable chemicals / biobased products

- Cuts to the Biomass Crop Assistance Program (BCAP), USDA/DOE Loan Guarantee Programs (LGP), and DOE Biomass Research and Development Program threaten to derail commercial, demonstration, and pilot biorefinery projects that are finally making progress after two years of credit freeze. As one of the most promising opportunities for high quality

domestic job creation, we should be increasing our investment in biorefinery projects, not cutting. BIO's industrial biotech funding priorities for FY12 are attached (see **Appendix R, S, T**).

- As we look to the next farm bill reauthorization, we need to ensure that these programs support the full range of biorefinery products. Some programs, such as the USDA LGP, need new legislative authority to include renewable chemicals and biobased products. Other programs are authorized to support these technologies, but have focused almost entirely on fuels. We need to make sure USDA and DOE ramp up their investment in renewable chemicals.

Farm Bill – Ensure robust energy title in Farm Bill reauthorization

- USDA has rightfully taken a leadership role in helping to commercialize advanced biofuels and biobased products through programs authorized under the farm bill's energy title (Title IX). These programs are just now realizing their full potential after protracted rulemaking (most of the programs only finalized rules late last year). We must ensure USDA has the tools it needs to succeed going forward by further strengthening these programs and identifying other ways USDA can help achieve the biobased economy. BIO's farm bill energy title priorities are attached as **Appendix U**.

DOD – Support DOD's Role in Advanced Biofuels Production

- Transportation fuel security is a national security issue, not just for the American public, but also for America's military. The Defense Department has expressed a desire to help address fuel security by facilitating the commercialization of military-grade advanced biofuels. DOD should be provided with all of the tools necessary to accomplish this mission. A joint letter from the advanced biofuels and commercial aviation industries in support of the recently announced Navy-USDA-DOE Memorandum of Understanding on Drop-in Biofuels is attached as **Appendix V**.

RFS - Support the Renewable Fuel Standard

- The federal Renewable Fuel Standard (RFS) is the fundamental policy supporting the development of the advanced biofuels industry. It provides both market assurance and a price premium for high-performing advanced biofuels, resulting in a strong investment case for advanced biofuels once investors gain sufficient confidence in the technology. BIO's analysis of value proposition for advanced biofuels under the RFS is attached as **Appendix W**. The Administration should reinforce its commitment to the national mandate of 21 billion gallons of advanced biofuels by 2022 as part of the overall RFS goal of 36 billion gallons. To stimulate necessary investment in advanced biofuel technologies, the market needs an unwavering message that the EPA will set annual advanced biofuels volumes at the level mandated in the Energy Independence and Security Act of 2007.

Tax – Incentivize innovation in tax code

- Tax policy can more effectively promote advanced biofuels commercialization by providing the long-term opportunity and flexibility available to other renewables such as wind and geothermal. An enduring package of advanced biofuels tax incentives that extends the cellulosic biofuel producer credit, expands feedstock eligibility, and allows developers to

elect either a producer credit or refundable investment tax credit should be pursued aggressively.

- The tax code should also incentivize commercialization of innovative renewable chemicals and biobased products, which have tremendous potential to create lasting, high-quality domestic jobs while revitalizing rural economies, improving balance of trade, and reducing GHG emissions.

BIO's 5-year plan incorporates many of these concepts and adds several additional innovative policy proposals to advance the biobased economy. The executive summary of the industrial biotech chapter of this proposal is included below and attached as **Appendix X**. Administration support of these proposals is strongly encouraged.

BIO Industrial & Environmental Section 5 Year Plan Proposal:
The Biobased Economy Jobs and Development Act

The "Biobased Economy" refers to economic activity and jobs generated by the use and conversion of agricultural feedstocks to higher value products, the use of microbes and industrial enzymes as transformation agents or for process changes and the production of biobased products and biofuels. This proposal seeks to elevate the concept and awareness of the biobased economy and advance the policy priorities of the IES working groups, highlighting the outstanding job creation and rural / rust belt economic development potential of industrial biotechnology and biorefinery commercialization.

SUMMARY

Title I – Agriculture

Biomass Crop Assistance Program – Reauthorization and Enhancement
BCAP is the key program encouraging and facilitating farmers and landowners to produce new purpose grown energy crops (PGECs) for advanced biofuels and biobased products. This section reauthorizes BCAP through December, 2017, and enhances the program by: (1) ensuring funds are directed primarily to production of next generation crops for biofuels and bioenergy; (2) establishing a dedicated funding mechanism for awarded contracts; (3) providing for eligibility of non-food Title I crops; and (4) clarifying eligibility of certain other PGECs.

Federal Crop Insurance for Purpose Grown Energy Crops
While the U.S. Department of Agriculture's (USDA) Risk Management Agency (RMA) is currently studying the feasibility of developing crop insurance programs for certain biofuels and bio-products feedstocks, there is no formal federal crop insurance program available to producers of new PGECs. This section directs the RMA to finalize its research and work with stakeholders to establish by January 1, 2013, a formal crop insurance program that will cover PGECs. Provides such sums as are necessary from the Commodity Credit Corporation to carry out these crop insurance objectives.

Feedstock Sustainability Enhancement Grants
The continued development of domestic sources of energy, including for biofuels and renewable chemicals, depends upon the sustainable availability of consistent, high yield, good quality feedstocks. This section establishes a grant program through the U.S. Departments of Agriculture and Energy to fund demonstration projects that utilize practices to enhance biofuel and bioenergy feedstock sustainability. Authorizes $50 million annually through 2017.

Farm Bill Energy Title Amendments for Renewable Chemicals
Many of the programs in the 2008 Farm Bill's Title IX renewable energy programs are not available to renewable chemicals and biobased products, despite their profound potential benefits to rural America. This section codifies the definition of renewable chemicals; modifies the section 9003 Biorefinery Assistance Program and 9007 Rural Energy for America Program to provide for eligibility of renewable chemicals projects; and expands the USDA BioPreferred program to increase program outreach and education.

Title II – Tax

Tax Credit for Production of Qualifying Renewable Chemicals
Renewable chemicals and biobased plastics represent an important technology platform for reducing reliance on petroleum, creating green US jobs, increasing energy security, and reducing greenhouse gas emissions. By providing a renewable chemicals tax credit, Congress can create jobs and other economic activity, and can help secure America's leadership in the important arena of green chemistry. This section provides a federal income tax credit for domestically produced renewable chemicals. Like current law renewable electricity production credits, the credits would be general business credits available for a limited period per facility. Similar to the operation of IRC section 48C, the Treasury Department and USDA would review taxpayers' applications in a competitive process to ensure conformance with legislative intent. Per calendar year, each taxpayer would be entitled to claim as much as $25MM in renewable chemicals production tax credit associated with production of eligible renewable chemicals.

Advanced Biofuels Tax Reform
Current tax law on advanced biofuels does not provide an ordered pathway toward U.S. energy security. Congress must consider amendments to the current law tax incentives that focus on bringing commercial volumes of affordable advanced biofuels to market in the near term. This section implements several changes to the tax code towards this end: (1) extend the Cellulosic Biofuel Production Tax Credit through 2016 and add eligibility for algal biofuels; (2) allow advanced biofuel facility developers the option of electing to receive an investment tax credit; (3) provide for eligibility of biorefinery retrofit projects; (4) provide eligibility to federal Section 1603 Grants in Lieu of Tax Credits program; and (5) extend and expand eligibility for cellulosic biofuel property accelerated depreciation.

Title III – Defense

Strategic Biorefinery Initiative and Offtake Authority
Substantial energy security benefits would accrue to the Department of Defense from development of domestic sources of renewable biofuels and biobased products. As a major potential customer and as a potential source of funding for biorefinery construction, the Department of Defense is uniquely positioned to help accelerate deployment of these vital products. This section establishes and provides necessary funding for a DoD Strategic Biorefinery Deployment Program to finance construction of the first 5 commercial military advanced biofuel biorefineries. It directs DoD to identify existing funding authority for such projects, and to conduct by January 1, 2012, a biorefinery "fly-off" to identify and fund construction of the most promising projects. In addition, this section provides DoD with the authority to enter into long-term (up to 15 years) offtake agreements for procurement of advanced biofuels for military use.

Title IV – Energy

Repurpose and Retrofit Grant Program
It is widely recognized that repurposing or retrofitting existing idled or underutilized U.S. manufacturing facilities to integrate next generation processes capable of producing advanced biofuels and renewable chemicals and bio-products is one of the most time and cost effective ways to build out the advanced biofuels and renewable chemicals sector. This section establishes a federal matching grant program through the U.S. Department of Energy to fund projects to repurpose or retrofit existing idle or underutilized manufacturing facilities for the production of advanced biofuels and/or renewable chemicals. Provides up to 30 percent of eligible costs. Authorized at $100 million annually through 2017.

Synthetic Biology for Enhanced Sustainability of Biofuels and Renewable Chemicals
The advancing field of synthetic biology has the potential to greatly enhance both the economic and environmental sustainability of fuels and chemicals manufacturing. This section establishes a DOE Synthetic Biology Research and Development (R&D) Grants Program to fund research and development in industrial biotechnology for the enhanced sustainability of biofuels and renewable chemicals produced through synthetic biology technology. This program would support work on biological catalysts and processes that enable the cost-effective sustainable production of advanced biofuels, renewable chemicals and other technologies that reduce or minimize greenhouse gas emissions, including biological processes for removing carbon dioxide from the atmosphere. Authorizes $20M annually for this program through 2017.

Industrial Bioprocess R&D Program
The use of industrial biotechnology for the production of renewable chemicals and biobased products is enabling dramatic improvements in industrial energy efficiency as well as a host of renewable alternatives to traditional petrochemical-based products. This section establishes an Industrial Bioprocess Research & Development (R&D) program through the DOE Office of Energy Efficiency and Renewable Energy (EERE), Industrial Technologies Program (ITP), to fund projects in industrial biotechnology for renewable chemicals, biobased products, and renewable specialty chemicals. Authorizes $150M annually through 2017.

Title V – Environment

EPA R&D Program for Renewable Chemicals
Renewable chemicals can be engineered to provide innovative solutions that save energy, are environmentally preferred, and are a direct substitute or “drop-in” replacement for petrochemicals. Presently, there are no strong standardized metrics to quantify environmental benefits of these innovative products. Standardized metrics would allow renewable chemical companies to demonstrate substantial cost, environmental, and efficiency benefits, further encouraging the development of sustainable products. This section establishes a new Research and Development (R&D) program funded by the Environmental Protection Agency (EPA) that would provide grants to conduct environmental assessments for renewable chemicals and industrial products produced with industrial biotechnology. This program would (1) conduct assessments to provide quantitative data to demonstrate chemical safety and pollution prevention in industrial biotechnology processes; and (2) be followed up with educational and awareness programs for U.S. businesses for the purpose of providing education and data on the environmental and economic benefit of using green chemistry and biological processes in manufacturing. Authorizes $30M annually through 2017.

UNLEASHING THE PROMISE OF BIOTECHNOLOGY

Advancing American Innovation to Cure Disease and Save Lives

TABLE OF CONTENTS

A SUMMARY OF BIO'S 5-YEAR STRATEGIC PLAN: RE-ENGINEERING THE BIOTECH ECONOMIC MODEL & RE-INVENTING THE IDEA-TO-MARKET PATHWAY

A. RE-ENGINEERING THE ECONOMIC MODEL

Research and development in the biotechnology industry is a high-risk undertaking because of the substantial start-up costs, lengthy experimentation period, and possibility that the technology will not be viable commercially or otherwise. Congress has historically provided tax incentives to high-risk industries (such as oil and gas, alternative energy, and high-tech start-ups) as a means for encouraging investment in new endeavors. Additionally, the Administration and Congress have repeatedly stated the importance of supporting innovation in health, renewable energy, and green technologies. However, current tax law does not reflect a cohesive strategy to foster growth for health, green technology, or energy-focused biotechnology companies. Given the potential economic and societal benefits of ensuring a robust biotechnology industry in the United States, it is imperative that Congress and the Administration adopt policies that recognize the unique financial structure and needs of biotechnology companies.

The proposals described below are designed to incentivize investors, strengthen small business, and promote innovation in the United States. There are proposals for early-, mid-, and late-stage companies across the biotechnology spectrum, as well as for larger pharmaceutical, biofuels, and renewable energy companies.

SMALL BUSINESS INVESTOR INCENTIVES

Incentivizing Small Biotech Investment: Angel Investor Tax Credit

Modeled after numerous state programs, a federal Angel Investor Tax Credit would provide an incentive for high net worth individuals to invest in emerging biotech companies. To be eligible for this credit, investors would have to make an investment in a company with fewer than 500 employees performing qualifying research. The credit would be equal to 50% of their investment, thus providing an important tax incentive for investment in innovative research-intensive industries.

Stimulating Private Capital for Biotechnology: R&D Partnership Structures

Due to the drawn out nature of the drug development process, small biotechnology companies often have difficulty obtaining early-stage financing for their research and development. Given that these smaller biotech companies are not yet profitable, they are unable to immediately use their tax assets to offset income. New partnership structures wherein biotech companies would enter into a joint venture with high net worth investors and flow through certain tax assets (i.e., tax credits and losses) from the biotech company or its projects to the investors would provide more immediate benefits by allowing investors to offset their income with the company's tax assets, thus stimulating private investment.

Improving Capital Gains Treatment for Small Businesses: Section 1202 Reform
Section 1202 of the Internal Revenue Code, which provides for a reduced capital gains rate for qualified investments in certain small business stock, is not currently beneficial to small biotech companies. Due to the valuable intellectual property and successive rounds of financing inherent in innovative industries, biotech companies do not meet the definition of qualified small businesses under Section 1202. Thus, the Section does not provide investors an incentive to invest in small biotech companies. Among other changes, modifications to the small business definition in Section 1202 would encourage investment in research performed by capital-intensive small biotech companies.

Doubling Private Funding: Small Business Early-Stage Investment Program
A small business early-stage investment program would provide matching grants to venture capitalists that specialize in funding small innovative companies. The government grants would match investments in targeted small businesses, including emerging biotech companies, essentially doubling their financing. Such funding would give start-up biotech companies important seed financing, while also enabling them to leverage the funding to spur further investment. The Board previously supported this policy when passed last year by the U.S. House of Representatives.

SMALL BUSINESS TAX INCENTIVES

Removing Financing Restrictions: Section 382 NOL Reform
Section 382 of the Internal Revenue Code restricts the usage of net operating losses (NOLs) by companies which have undergone an "ownership change." The law was enacted to prevent NOL trafficking, but small biotech companies are caught in its scope – their reliance on outside financing and deals triggers the ownership change restrictions. Reform of Section 382 would include two provisions: (1) exempting NOLs generated by qualifying research and development by a small business from Section 382; and (2) redefining "ownership change" to exclude certain qualified investments, like those in rounds of venture financing. If small biotech companies could retain their NOLs, they would be able to include them as tax attributes on the balance sheet, thus increasing their value when preparing for additional rounds of financing like mergers or initial public offerings.

INCENTIVES FOR NON-INVESTOR CAPITAL

Increasing R&D Investment: Repatriation
Many small biotechnology companies rely on collaborations with large multi-national corporations to fund their research and development. A repatriation tax holiday on funds brought back to the United States from abroad would incentivize these large companies to repatriate earnings they are holding overseas, and give them the ability to invest in and collaborate with small biotech companies conducting ground-breaking research.

Rewarding Innovative R&D Businesses: U.S. Innovation Box
Many Western European countries have implemented an innovation box that provides for a reduced corporate tax rate on income stemming from certain types of intellectual property, the

lifeblood of the biotechnology industry. Allowing for a reduced corporate rate on this type of income would make investment in U.S. biotechnology more attractive and provide innovative companies with a greater return on their R&D expenses, allowing them to undertake more research projects in the United States.

Supporting Industry Collaborations: Section 197 Amortization Reform
Tax incentives, such as accelerated amortization, can encourage large company investors contemplating acquisitions of specific intangible assets of small biotech companies to invest at an earlier stage in the company's research. Small biotech companies typically have intangible assets that are amortizable under Section 197 of the Internal Revenue Code; thus, reforming that Section to provide for faster cost recovery for intangible assets acquired by investors would stimulate early-stage investment in these companies.

POLICIES TO STIMULATE A BIO-BASED ECONOMY

The "Bio-based Economy" refers to economic activity and jobs generated by the use and conversion of agricultural feedstocks to higher value products, the use of microbes and industrial enzymes as transformation agents or for process changes, and the production of bio-based products and biofuels. The proposals below seek to elevate the concept and awareness of the bio-based economy and advance the policy priorities of the Industrial & Environmental Section (IES) working groups, highlighting the outstanding job creation and rural/rust belt economic development potential of industrial biotechnology and biorefinery commercialization.

Agriculture

Biomass Crop Assistance Program (BCAP) – Reauthorization and Enhancement
BCAP is the key program encouraging and facilitating farmers and landowners to produce new purpose grown energy crops (PGECs) for advanced biofuels and bio-based products. This proposal would reauthorize BCAP through December 2017, and enhance the program by: (1) ensuring funds are directed primarily to production of next-generation crops for biofuels and bioenergy; (2) establishing a dedicated funding mechanism for awarded contracts; (3) providing for eligibility of non-food Title I crops; and (4) clarifying eligibility of certain other PGECs.

Federal Crop Insurance for Purpose Grown Energy Crops
While the U.S. Department of Agriculture's (USDA) Risk Management Agency (RMA) is currently studying the feasibility of developing crop insurance programs for certain biofuels and bio-products feedstocks, there is no formal federal crop insurance program available to producers of new PGECs. This proposal would direct the RMA to finalize its research and work with stakeholders to establish by January 1, 2013, a formal crop insurance program that will cover PGECs, and would authorize such sums as are necessary from the Commodity Credit Corporation to carry out these crop insurance objectives.

Feedstock Sustainability Enhancement Grants
The continued development of domestic sources of energy, including for biofuels and renewable chemicals, depends upon the sustainable availability of consistent, high yield, good quality

feedstocks. This proposal would establish a grant program through USDA and the U.S. Department of Energy (DOE) to fund demonstration projects that utilize practices to enhance biofuels and bioenergy feedstock sustainability, and authorize $50 million annually through 2017 for such purposes.

Farm Bill Energy Title Amendments for Renewable Chemicals
Many of the programs in the 2008 Farm Bill's Title IX renewable energy programs are not available to renewable chemicals and bio-based products, despite their profound potential benefits to rural America. This proposal would codify the definition of renewable chemicals; modify the Section 9003 Biorefinery Assistance Program and the Section 9007 Rural Energy for America Program to provide for eligibility of renewable chemicals projects; and expand the USDA BioPreferred program to increase program outreach and education.

Tax

Tax Credit for Production of Qualifying Renewable Chemicals
Renewable chemicals and bio-based plastics represent an important technology platform for reducing reliance on petroleum, creating green U.S. jobs, increasing energy security, and reducing greenhouse gas emissions. By providing a renewable chemicals tax credit, Congress can create jobs and other economic activity, and can help secure America's leadership in the important arena of green chemistry. This proposal would provide a federal income tax credit for domestically produced renewable chemicals. Like renewable electricity production credits in current law, these new credits would be general business credits available for a limited period per facility. Similar to the operation of Internal Revenue Code Section 48C, the Treasury Department and USDA would review taxpayers' applications in a competitive process to ensure conformance with legislative intent. Per calendar year, each taxpayer would be entitled to claim as much as $25 million in renewable chemicals production tax credit associated with production of eligible renewable chemicals.

Advanced Biofuels Tax Reform
Current tax law on advanced biofuels does not provide an ordered pathway toward U.S. energy security. Congress should consider amendments to current law tax incentives that focus on bringing commercial volumes of affordable advanced biofuels to market in the near term. This proposal would implement several changes to the tax code towards this end: (1) extend the Cellulosic Biofuels Production Tax Credit through 2016 and add eligibility for algal biofuels; (2) allow advanced biofuels facility developers the option of electing to receive an investment tax credit; (3) provide for eligibility of biorefinery retrofit projects; (4) provide eligibility to the federal Section 1603 Grants in Lieu of Tax Credits program; and (5) extend and expand eligibility for cellulosic biofuels property accelerated depreciation.

Defense

Strategic Biorefinery Initiative and Offtake Authority
Substantial energy security benefits would accrue to the U.S. Department of Defense (DOD) from development of domestic sources of renewable biofuels and bio-based products. As a major potential customer and as a potential source of funding for biorefinery construction, DOD

is uniquely positioned to help accelerate deployment of these vital products. This proposal would establish and provide necessary funding for a DOD Strategic Biorefinery Deployment Program to finance construction of the first five commercial military advanced biofuels biorefineries. It directs DOD to identify existing funding authority for such projects, and to conduct by January 1, 2012, a biorefinery "fly-off" to identify and fund construction of the most promising projects. In addition, this proposal would provide DOD with the authority to enter into long-term (up to 15 years) offtake agreements for procurement of advanced biofuels for military use.

Energy

Repurpose and Retrofit Grant Program
It is widely recognized that repurposing or retrofitting existing idled or under-utilized U.S. manufacturing facilities to integrate next-generation processes capable of producing advanced biofuels and renewable chemicals and bio-products is one of the most time and cost effective ways to build out the advanced biofuels and renewable chemicals sector. This proposal would establish a federal matching grant program through DOE to fund projects to repurpose or retrofit existing idle or under-utilized manufacturing facilities for the production of advanced biofuels and/or renewable chemicals, up to 30 percent of eligible costs. It would authorize $100 million annually through 2017.

Synthetic Biology for Enhanced Sustainability of Biofuels and Renewable Chemicals
The advancing field of synthetic biology has the potential to greatly enhance both the economic and environmental sustainability of fuels and chemicals manufacturing. This proposal would create a DOE Synthetic Biology Research and Development Grants Program to fund research and development in industrial biotechnology for the enhanced sustainability of biofuels and renewable chemicals produced through synthetic biology technology. This program would support work on biological catalysts and processes that enable the cost-effective sustainable production of advanced biofuels, renewable chemicals, and other technologies that reduce or minimize greenhouse gas emissions, including biological processes for removing carbon dioxide from the atmosphere. The proposal would authorize $20 million annually for this program through 2017.

Industrial Bioprocess R&D Program
The use of industrial biotechnology for the production of renewable chemicals and bio-based products is enabling dramatic improvements in industrial energy efficiency, as well as a host of renewable alternatives to traditional petrochemical-based products. This proposal would create an Industrial Bioprocess Research & Development program through the DOE Office of Energy Efficiency and Renewable Energy's Industrial Technologies Program, to fund projects in industrial biotechnology for renewable chemicals, bio-based products, and renewable specialty chemicals. It would authorize $150 million annually for this program through 2017.

Environment

EPA R&D Program for Renewable Chemicals
Renewable chemicals can be engineered to provide innovative solutions that save energy, are environmentally preferred, and are a direct substitute or "drop-in" replacement for petrochemicals. Presently, there are no strong standardized metrics to quantify environmental benefits of these innovative products, and allow renewable chemical companies to demonstrate substantial cost, environmental, and efficiency benefits, further encouraging the development of sustainable products. This proposal would establish a new Research and Development grant program funded by the Environmental Protection Agency (EPA) that would provide grants to conduct environmental assessments for renewable chemicals and industrial products produced with industrial biotechnology. This program would (1) conduct assessments to provide quantitative data to demonstrate chemical safety and pollution prevention in industrial biotechnology processes; and (2) be followed up with educational and awareness programs for U.S. businesses for the purpose of providing education and data on the environmental and economic benefit of using green chemistry and biological processes in manufacturing. It would authorize $30 million for this program annually through 2017.

B. Re-Inventing the Idea-to-Market Pathway

Creating a 21st Century FDA

The proposals below are designed to ensure a clear and effective pathway for turning ideas into realities that will benefit patients and improve public health. The proposals are focused on creating a 21st century U.S. Food & Drug Administration (FDA), and creating more effective clinical research and development processes. With an increasingly aging population, it has never been more critical to support an industry that offers solutions to the most pressing health care needs of today and tomorrow. It is imperative that FDA be an agency that recognizes its national role in advancing innovation, maintains the ability to effectively review innovative products in a timely manner, and promotes a consistent and science-based decision making process that is reflective of patient needs. The proposals described below are designed to address each of these principles. They are organized under three main headings: Elevating FDA and Empowering Operational Excellence; Advancing Regulatory Science and Innovation; and Enabling Modernized Patient-Centric Clinical Development.

Elevating FDA and Empowering Operational Excellence

Update the FDA Mission Statement
FDA needs a clear mandate to encourage the development of innovative products. In addition, FDA must have the capacity and commitment to incorporate the latest scientific advances into its decision making so that regulatory processes can keep pace with the tremendous potential of companies' leading edge science. Congress can help by updating FDA's statutory mission to underscore the need for FDA to advance medical innovation by incorporating modern scientific tools, standards, and approaches into the agency's work, so that innovative products can be made available to those who need them and in a timely manner.

Establish a Fixed Term of Office for the Commissioner of Food and Drugs

The Commissioner of Food and Drugs is charged with leading a science-based, regulatory agency to advance the public health. As required by statute, the President appoints the Commissioner with the advice and consent of the U.S. Senate. However, a presumption of replacement with each new President has politicized the appointment and confirmation process. The Federal Food, Drug, and Cosmetic Act (FFDCA) should be amended to provide that the President appoint the Commissioner to a six-year term of office. Once confirmed, the Commissioner would be removable by the President only for pre-specified reasons – neglect of duty, malfeasance in office, or an inability to execute the agency's mission. Encouraging consistent and stable leadership at FDA, with protection from political influence that typically occurs during a presidential administration transition, better equips the agency to fulfill its mission to protect and promote the public health.

Grant FDA Status as an Independent Agency

FDA regulates nearly a quarter of the consumer goods supplied to the American public. As such, the agency should have the same authorities to make budget, management and operational decisions as afforded other independent agencies such as the Environmental Protection Agency. This would empower the agency to work more effectively with the President and Congress to carry out its mission to promote and protect the public health. Creating an independent agency would also enhance the agency's ability to obtain quality and consistent leadership.

Establish an External Management Review Board for FDA

FDA is a large, complex organization, and in order to fulfill its responsibilities effectively, it must be well organized and well managed. It is critical that the agency's organization and management capabilities be periodically analyzed, and that the Commissioner of Food and Drugs be provided with fresh, visionary, and independent thinking on how to improve the ability of the agency and its centers to promote and protect the public health, as well as the support necessary to implement recommendations. An external advisory board composed of individuals with experience in organizational management could help the agency address operational challenges. Current law should be amended to establish a Management Review Board (MRB) to conduct periodic reviews of FDA's management and organizational structure, and to provide recommendations to the Commissioner about ways to improve FDA operations.

ADVANCING REGULATORY SCIENCE & INNOVATION

Support Regulatory Science Public-Private Partnerships

Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress established the Reagan-Udall Foundation for the Food and Drug Administration, an independent non-profit organization intended to support public-private partnerships for the purpose of advancing the mission of FDA to "modernize medical [and other] product development, accelerate innovation, and enhance product safety." The Foundation could, for example, form collaborations to advance the use of biomarkers, surrogate markers, and new trial designs to improve and speed clinical development. However, Congressional appropriations bills for the

agency have subsequently restricted FDA's ability to transfer federal funding to the Foundation. These funding restrictions should be lifted so that the Reagan-Udall Foundation can fulfill its promise.

Create an FDA "Experimental Space," led by a Chief Innovation Officer, to Pilot Promising New Scientific and Regulatory Approaches

FDA has developed several initiatives to advance regulatory science. These include the FDA/NIH Joint Leadership Council, the academic Centers of Excellence in Regulatory Science, and FDA's Critical Path Initiative. However, FDA's ability to incorporate modern science into its regulatory processes has been limited because there is no entity within the agency with unified responsibility for systematically analyzing the findings and recommendations from these groups, and with clear authority to pilot promising scientific and regulatory approaches. An FDA "Experimental Space," led by a new Chief Innovation Officer, should be established with the responsibility and authority to ensure that promising new approaches are integrated into agency operations at all levels.

Enhance FDA's Access to External Scientific and Medical Expertise

FDA is the preeminent federal agency charged with evaluating cutting-edge science as it is applied to the prevention, diagnosis, and treatment of human disease. FDA also has been perceived by many as the global standard bearer for regulatory review of drug and biologic applications. However, scientific and medical knowledge, techniques, and technology are advancing at a more rapid pace today than at any other time, and FDA's capacity to access information about these advances has not kept pace. It is essential that FDA's access to scientific and medical advice be enhanced by improving the operations of FDA Advisory Committees, establishing Chief Medical Policy Officers in the immediate offices of the Center Directors, and providing FDA staff with additional avenues for accessing external scientific and medical expertise.

ENABLING MODERNIZED PATIENT-CENTRIC CLINICAL DEVELOPMENT

Increase Access to Innovative Treatments and Therapies through Progressive Approval

Patients, industry, Congress, and others are eager to find ways to deliver safe and effective new drugs and biologics to patients. Patients, particularly those with illnesses for which no adequate therapy exists, want access to promising new therapies earlier in the drug development process. Smaller biopharmaceutical companies that develop those therapies are sometimes unable to maintain operations through extensive phase III testing without revenue from the sale of products. Expanding and improving the accelerated approval pathway into a progressive approval mechanism would help provide patients more timely access to needed therapies. This pathway would be limited to innovative products for unmet medical needs, significant advances to standard of care, targeted therapies, and those that have been approved by the European Medicines Agency (EMA) or other mature regulatory agencies. This pathway also would ensure risk-benefit analysis that incorporates the safety and needs of patients in the real world.

Empower FDA to Utilize a Weight-of-Evidence Approach
FDA's current statutory authority requires that the agency approve applications for new drugs when they have been demonstrated to be safe and effective under the intended conditions of use. The law provides that effectiveness is established where FDA is satisfied that there is "substantial evidence" that the new drug has the intended effect that it is purported to have. FDA typically requires two "adequate and well controlled" studies under this standard. A weight-of-evidence approach to data analysis, however, would allow the decision-maker to look at all data and information, whatever its value, and give each appropriate consideration.

Leverage Electronic Health Records to Facilitate Clinical Research
Every new drug's sponsor spends years designing and conducting clinical trials to show the drug is safe and effective. Using health information technology (IT) such as electronic health records (EHRs) in clinical research will improve and speed up the drug development process, and decrease costs. However, there are significant barriers preventing wide-spread use of health IT in clinical research, including slow adoption by providers and lack of standards development. FDA can help remove those barriers. Congress should create a Clinical Informatics Coordinator in the Office of the Commissioner of Food and Drugs charged with developing processes to validate and encourage the use of health IT in clinical research, and establishing pilot projects to use health IT in clinical research.

Require FDA to Disclose to the Sponsor Reasons for Non-Approval
The Federal Food, Drug, and Cosmetic Act (FFDCA) implies that licensing or approval applications are a binary question – approve or deny – due to phased, investigational review of applications; however, there is in practice a third response. In this case, FDA neither approves nor officially denies the application (which would require FDA to give the sponsor specific procedural rights such as a hearing); rather it finds the application to be incomplete in some way that makes the application ineligible for approval. When FDA makes such a finding, it should communicate to sponsors in clear terms why risk was determined to outweigh benefits, and why other agency authorities such as Risk Mitigation and Evaluation Strategies (REMS) – which are designed to mitigate risk for approved products – are insufficient (in addition to indicating what must be done to address any deficiencies). Such an approach would help create a consistent and transparent evaluation of risk-benefit, and provide the sponsor with better information on what, if any, additional studies are required to achieve approval.

THE ROAD TO A BRIGHTER FUTURE FOR AGRICULTURAL BIOTECHNOLOGY

For the past two decades, the United States has played a leadership role in agricultural biotechnology innovation, contributing billions of dollars to the U.S. GDP. Unfortunately, the U.S. regulatory system for plant and animal biotechnology, which was designed in the mid-1980s to facilitate product development, is fast becoming an impediment to the development and commercialization of safe, beneficial products. Today, developers of agricultural biotechnology are less certain about the length and scope of federal regulatory approvals and the susceptibility of approvals to legal challenge. Greater certainty is needed to drive scientific innovation and reassure international trading partners, which is essential to U.S. producers of genetically-engineered products. While the underlying statutory authorities and regulatory framework for

agricultural biotechnology are sound, to improve the process it will be important for Congress to give necessary direction to the federal agencies responsible for implementing the governing statutes that most directly impact genetically-engineered plants and animals. BIO therefore will propose a series of appropriate directives for the Congress to enact.

ATTACHMENT I: CAPITAL FORMATION POLICIES

SMALL BUSINESS INVESTOR INCENTIVES

ANGEL INVESTOR TAX CREDIT

Background

There is no federal income tax credit for investments in small businesses by the "angel investors" that bridge the gap between friends-and-family financing and venture capital funds. This "early-stage" or "seed" capital is vital to fund the operations of start-up ventures, especially in capital intensive industries such as biotechnology. For biotechnology companies, the lengthy time period from research and development to commercialization requires "patient capital" – investors who have a longer term investment horizon to achieve their desired economic returns. This is because those companies do not generate profits to fund operations and have little access to debt financing. Such patient capital often comes from angel investors.

Many states have recognized that a state income tax credit is an effective incentive to increase investment by angel investors. Currently, more than 20 states have some form of an angel investor tax credit. In general, the credit amounts have ranged from 25% to 50% of the qualified investment (with one state, Hawaii, providing a 100% tax credit). These programs often have a cap on the amount of credit available per investor or per company. Also, many states curtail the cost of the credit by maintaining a cap on the total amount of credits that the state will give out. Such provisions limit the revenue cost of these incentive programs.

A federal angel investor income tax credit ("Angel Investor Tax Credit") would provide a tax credit for individuals investing in certain qualified small companies, such as biotechnology start-ups. The tax credit could be used by the individual to offset other income tax liability, thus decreasing the angel investor's overall tax liability and freeing up additional investment capital. Thus, the Angel Investor Tax Credit would incentivize high net worth individuals to invest in small biotechnology and other companies, providing these companies with critical funding.

Proposed Federal Angel Investor Tax Credit

The Angel Investor Tax Credit would be available to qualified angel investors making a qualified equity investment directly or through a qualified fund in an eligible small business. The credit would be nonrefundable and would not be subject to limits on its use for alternative minimum tax purposes.

Qualified Angel Investor

To take advantage of the Angel Investor Tax Credit, the qualified equity investment would have to be made by an individual that is an "accredited investor" for SEC purposes. Such accredited investors include a natural person who has an individual net worth, or joint net worth with their spouse, that exceeds $1 million, and a natural person with income exceeding $200,000 in each of the two most recent years or joint income with a spouse exceeding $300,000 for those years and a reasonable expectation of the same income level in the current year. In addition, a qualified equity investment could be made by a "qualified fund", which would be defined as (A) a pass-

through entity (*i.e.*, an S corporation, tax partnership, etc.) formed and operated for the purpose of making equity investments in an eligible small business and (B) of which all the shareholders, partners or members are individuals who are "accredited investors" for SEC purposes. A qualified angel investor would not include a person controlling (directly or indirectly) 50% or more of an eligible small business, or an employee of such business. For purposes of clarity, a person would not fail to be a qualified angel investor solely on account of serving as a director of the company or entering into a *bona fide*, arm's-length consulting agreement.

Qualified Equity Investment

The taxpayer would generate an income tax credit with respect to each "qualified equity investment." A qualified equity investment is the acquisition of any equity interest (whether stock, partnership interest, limited liability company membership interest, etc.) at original issuance (either directly or through an underwriter) in an eligible small business.

Eligible Small Business

The Angel Investor Tax Credit would be available to qualified angel investors investing in an eligible small business, which is a business entity that meets the following criteria:

1. Either (a) the average annual number of full-time equivalent employees employed by the company during either of the two preceding years was 500 or fewer under Section 41(b)(3)(D)(iii) or (b) a corporation or other company that would (if treated as a "C" corporation for federal tax purposes) meet the definition of a qualified small business under Section 1202(d), substituting a $150 million gross asset test (with special rules for taking into account intangible assets of the company).

2. 50% of the company's employees must perform substantially all of their work in the United States and the headquarters must be located in the United States.

3. Conducts a specified amount of research and development. The research and development criterion would be based on the existing Section 41 research credit. Thus, the company's research and development activities would need to meet the "qualified research" definition under Section 41(d)(1)(B). Specifically, the project would need to focus on research activities undertaken for the purpose of discovering information—

    - which is technological in nature, and
    - the application of which is intended to be useful in the development of a new or improved business component of the taxpayer.[1]

4. Has been in existence for 5-years or less at the time of the qualified equity investment.

[1] The research and development requirement would also incorporate the standards used by the IRS in determining whether there is "qualified research" under Section 41(d) (*e.g.*, uncertainty, related to development/improvement, etc.), with appropriate modifications for purposes of this provision.

Angel Investor Tax Credit Amount and Limitations
The amount of the Angel Investor Tax Credit would equal 50% of the qualified angel investor's qualified equity investment. The amount of the tax credit would be subject to limitations as follows:

- An individual/married couple would be capped as to the aggregate amount of the Angel Investor Tax Credit per eligible small business in a single taxable year.
- An individual/married couple would be capped at the total amount of Angel Investor Tax Credits in all eligible small businesses in a single taxable year.
- The aggregate amount of Angel Investor Tax Credits per eligible small business in a taxable year would be capped.
- The aggregate amount of Angel Investor Tax Credits per eligible small business would be capped at a maximum amount.

Other Rules
The Angel Investor Tax Credit would be part of the general business credit of Section 38 and treated as a specified credit for such purposes (*i.e.*, removing the AMT limitation otherwise applicable to general business credits). Controlled group rules would apply for purposes of determining whether commonly-owned business entities that were eligible small businesses on a stand-alone basis would qualify as such if aggregated. The credit would be subject to recapture as a result of certain recapture events, such as a sale or exchange of the qualified equity investment within three years of that investment. The qualified equity investor's tax basis in their equity interest that is a qualified equity investment would be reduced by the amount of the Angel Investor Tax Credit.

Benefits of Angel Investor Tax Credit Proposal

Incentive for High Net Worth Individuals to Increase Investment
The tax credit would decrease the risks associated with investing in a small research-intensive company because it would provide immediate tax benefits that would free up additional capital that can be invested in the high-tech businesses.

Incentive for Critical Early-Stage/Seed Investment
The proposal would motivate individual angel investors to increase their investments at the seed/early-stage level. This would help close the "capital gap" that start-up companies currently face. This capital gap is especially prevalent for companies with equity investment needs in the $250,000 to $5 million range. Below that level, entrepreneurs rely on credit cards, second mortgages, and friends-and-family investments. At higher levels of funding, venture capital funds may invest. But for smaller companies, the capital gap at this critical range is vital to the commencement and expansion of their business. The tax credit would provide funding to earlier stage companies that is not currently available through the traditional venture capital process because venture capital investors typically do not invest at such an early stage.

Promotion of Innovation in Multiple Industries
Individual investors and qualified funds will only receive the credit if they invest in small, American companies engaged in Section 41(d) research and development. Many of these types of companies are emerging biotechnology and life sciences companies. However, the proposal extends the tax incentive more broadly than biotech companies. Thus, the proposal is ideal for coalition building, as other innovative industries that qualify under Section 41(d) (high tech, green tech, etc.) would also benefit from more early-stage investment.

The Benefits of Angel Investing Reward Society
Studies show that research and development has historically been underfunded because social returns may exceed private returns. Thus, the enactment of the Angel Investor Tax Credit would effectively act as a public-private partnership, which would provide significant positive externalities to society and not just benefit the angel investors.

R&D PARTNERSHIP STRUCTURES
PART 1: TAX INCENTIVES FOR SMALL BIOTECHNOLOGY INVESTMENTS

Background
Congress has historically provided tax incentives to high-risk industries (such as oil and gas, alternative energy, and high-tech start-ups) as a means for encouraging investment in new endeavors. The oil and gas industry is a primary example, where it is often necessary to invest significant amounts of capital to determine whether a particular well will be successful. Tax incentives have been provided to mitigate the geologic risk and the uncertain cash flows from oil and gas projects by enhancing the after-tax returns from the projects. In certain cases, Congress has restricted the tax incentives in a manner that provides the tax benefits to smaller producers that are less able to diversify the economic risks that inhere in oil and gas exploration.

The challenges faced by smaller producers in the oil and gas industry in finding and developing new resources and diversifying risk is analogous to the challenges faced by small life sciences companies. Small life sciences companies expend substantial financial resources on research and development of technology before successful FDA approval. In many cases, the projects may be the technological equivalent of a "dry well" and may not prove technologically or commercially viable.

There exist generally available tax incentives in the Code that can benefit companies in the biotechnology industry. For example, Section 41 provides a research tax credit for increases in qualifying research activities and Section 174 provides an immediate deduction for qualifying research and experimental expenditures.[2] These tax incentives are not specifically targeted to small biotechnology start-ups and generally are of little use to such companies organized as "C" corporations or as pass-through entities owned by individuals. "C" corporation start-ups often incur large net operating losses and do not generate the taxable income necessary to utilize losses and credits. Instead, the "C" corporation carries the tax attributes forward as deferred tax assets

[2] All "Section" or "§" references are to sections of the Internal Revenue Code of 1986, as amended, or the Treasury Regulations promulgated there under.

that may be used at some (distant) point in the future, provided that they are not in the interim subjected to limitation (*e.g.*, Section 382, which can severely restrict the value of loss carry-forwards). For individual owners of start-ups organized as pass-through entities, the passive activity loss rules of Section 469 impose restrictions on the ability to offset unrelated income with losses.

Even where start-up biotech companies are "C" corporations with taxable income or where individual owners of pass-through entities have the ability to take advantage of these incentives, the general tax credit and deduction provisions contain limitations that make them less effective as an incentive. Section 41 provides a credit only for incremental increases in research under a formula. For individuals, Section 174 expenditures are not fully deductible against the alternative minimum tax. The passive activity loss rules also defer the use of losses and tax credits generated. More recently, Congress enacted a credit more specific to the biotechnology industry, albeit narrowly drafted. The Code provided a credit for qualified investments in qualifying therapeutic discovery projects in Section 48D. However, the provision had a sunset date at the end of 2010.

Tax incentives for the biotechnology industry still can be useful where the start-ups are organized as "C" corporations with taxable income or are organized as pass-through entities (*e.g.*, tax partnerships) and the individual owners are able to use losses and credits, taking into account restrictions under the passive activity loss rules and other restrictions. Tax incentives are also useful for "C" corporation investors that can or do invest in biotech start-ups organized as pass-through entities because such investors that have taxable income can use the tax losses and credits generated by the start-up.

The present proposal would provide further incentives for start-up "C" corporation biotechnology companies and investors in pass-through biotechnology start-ups by providing tax benefits modeled after those available in the oil and gas industry. The types of tax incentives available to the oil and gas industry would be equally beneficial to (and are adaptable to) the life sciences industry, because the incentives would increase investment and attract new investment to this important activity.

Existing Tax Incentives for the Oil and Gas Industry

Tax incentives that apply to the oil and gas industry include the following:

1. Deduction of Intangible Drilling Costs: Oil and gas investors can immediately deduct intangible drilling costs ("IDCs"), which include many of the costs necessary for drilling the well (other than tangible equipment costs). Section 263(c). These expenses generally constitute a significant portion of the pre-production costs of drilling a well.
2. Depletion: Oil and gas investors can choose (subject to various restrictions) their method for recovering the costs of an oil and gas project. The two available methods are "percentage depletion" and "cost depletion." Section 611 *et seq*. The taxpayer may use whichever method provides for a higher deduction, providing the ability to accelerate deductions.

3. Passive Activity Loss Exception: The passive activity loss rules are an anti-tax shelter measure intended to curtail abusive transactions involving passive investments by individuals and certain other taxpayers. Congress provided an exception in these rules for working interests in oil and gas projects, which exception enables an investor to deduct losses from working interests even if the taxpayer does not "materially participate" in the activity. Section 469(c)(3). The ability of individual investors to offset these losses against other forms of income enhances their after-tax returns.
4. Geological and Geophysical Costs: These costs are amortizable over a 24-month period (7-years for major integrated oil companies). Section 167(h).
5. AMT Relief: There is favorable alternative minimum tax treatment of IDCs and depletion for independent producers. Section 57(a)(1).
6. Tax Credits: Tax credits are available for production of oil and gas from marginal wells and for various oil recovery methods. Sections 45I and 43.
7. Deduction for Qualified Tertiary Injectant Expenses: Certain types of injectant expenses are deductible, subject to limitations. Section 193.
8. Publicly-Traded Partnerships: Partnerships and limited liability companies that are publicly-traded are generally taxed as "C" corporations, which are not "flow-through" entities for tax purposes. There is an exception to these rules for entities that have sufficient amount of income from certain types of investments, including income from oil and gas sources. Section 7704(d).

Proposal for Biotechnology Incentives

Targeted tax incentives in the oil and gas industry increase the after-tax returns of investors by providing, *e.g.*, accelerated deductions, tax credits and special alternative minimum tax treatment. These types of tax incentives could similarly be applied in the biotechnology industry.

The proposal would follow the model of the taxation of the oil and gas industry and provide targeted tax incentives for biotechnology sector investments. The tax incentives would be available to projects that meet the definition of a small biotechnology business.

Small Biotechnology Business Definition

Under the proposal, a taxpayer that invests in a company that qualifies as a specially-defined "small biotechnology business" would be eligible for targeted tax incentives. A small biotechnology business would be defined as: (1) any flow-through entity if the annual average number of employees employed by such person during either of the 2 preceding calendar years was 500 or fewer under Section 41(b)(3)(D)(iii) or (2) a company that, if treated as a "C" corporation for federal tax purposes, meets the definition of a qualified small business under Section 1202(d), substituting a $150 million gross asset test (with special rules for taking into account intangible assets of the company). Controlled group rules would apply to ensure that the tax incentives were being generated by small biotechnology businesses.

Qualified Biotechnology Research and Development

In order to be eligible under this proposal, the small biotechnology business must conduct "qualified biotechnology research and development" in an amount that meets a minimum threshold amount.

The research and development prong would build off of the existing Section 41 research credit. Thus, the company's activities would need to meet the "qualified research" definition under Section 41(d)(1)(B). Specifically, the project would need to focus on research activities undertaken for the purpose of discovering information—

- which is technological in nature, and
- the application of which is intended to be useful in the development of a new or improved business component of the taxpayer.

This prong would also incorporate the standards used by the IRS in determining whether there is "qualified research" under Section 41(d) (*e.g.*, uncertainty, related to development/improvement, etc.), with appropriate modifications for purposes of this provision.

The biotechnology portion of the test would provide that the research and development conducted by the company must be in a recognized biotechnological field. This would be defined as a project designed to:

- Treat or prevent diseases or conditions by conducting pre-clinical activities, clinical trials, and clinical studies, or carrying out research protocols, for the purpose of securing FDA approval of a product under section 505(b) of the Federal Food, Drug, and Cosmetic Act or section 351(a) of the Public Health Service Act.
- Diagnose diseases or conditions or to determine molecular factors related to diseases or conditions by developing molecular diagnostics to guide therapeutic decisions.
- Develop a product, process, or technology to further the delivery or administration of therapeutics.
- Develop other projects in the biotechnology industry.

The minimum threshold amount of qualified biotechnology research and development would require that substantially all of the business activity of the company would consist of conducting research and development in the biotechnology field. "Substantially all" would be determined based on appropriate measures that are suitable for research and development small businesses, such as a specified ratio of research and development expenditures to product revenues.

Small Biotechnology Business Tax Incentive Proposals

First, there would be a tax credit for expenditures in biotechnology projects that would either be modeled after the qualified therapeutic discovery project credit as a stand-alone provision or incorporated within the framework of the Section 41 research credit. The amount of the credit would be based on 50% of the qualifying expenditures in the project, as determined under specified conditions, and it would not be an incremental credit as presently applies under Section 41.

Second, to the extent that biotechnology companies are presently required to capitalize costs and depreciate or amortize those costs over a lengthy recovery period, small biotechnology businesses would be permitted to accelerate the depreciation and amortization deductions. This provision would be similar to, but broader than, the deduction currently permitted under Section

174 for research and experimental expenditures. This tax incentive would be modeled after the IDC deduction currently permitted to oil and gas producers and would be intended to similarly incentivize investors in biotechnology projects.

Third, the proposal would enact, for individuals, an exception to the alternative minimum tax rules for specified biotechnology research and experimental expenditures.

Each of these amendments would be available to, and encourage investment in the biotechnology sector by, individuals who are able to use such tax benefits taking into account the passive activity loss rules and "C" corporation biotechnology start-ups that have taxable income. Other investors (for example, "C" corporations who invest in a pass-through small biotechnology business, but do not cause the company to fail to qualify as a small biotechnology business) could also take advantage of these tax incentives.

Other Considerations

The statutory amendments and relevant legislative history would provide that tax benefits from investments in these small biotechnology businesses would not be disallowed under the economic substance doctrine of Section 7701(o) and case law or Section 183 (the hobby loss rules) solely as a result of start-up losses incurred by such businesses. The proposal would also contain aggregation rules based on existing Code provisions that treat separate entities as being under "common control" in order to ensure that taxpayers do not inappropriately set up separate research and development companies intended to qualify as small biotechnology businesses.

R&D Partnership Structures
Part 2: Passive Activity Loss Exception

Background

Research and development in the biotechnology industry is a high-risk undertaking because of the substantial start-up costs, lengthy experimentation period, and possibility that the technology will not be viable commercially or otherwise. This industry shares many similarities to the oil and gas industry, where exploration, development, and commercialization of new petroleum-based resources has comparable risks. These risks are compounded for smaller biotechnological companies, just as they are for smaller oil and gas companies, because of the inability to spread the risk of failure across a broad number of projects.

Tax incentives in the oil and gas industry include favorable depreciation and amortization regimes (*e.g.*, deduction of intangible drilling costs, depletion, geological and geophysical cost amortization), tax credits for certain types of production, exceptions from the publicly traded partnership rules for oil and gas investments, alternative minimum tax relief associated with certain tax incentives, and, the subject of this proposal, an exception from the passive activity loss rules for certain oil and gas investments.

The passive activity loss rules were designed to thwart tax shelters that had developed by the mid-1980s for marketing to individuals. Congress enacted provisions that allowed losses from passive investment activities to only offset passive income (other than portfolio income from

investment-type activities). This limitation applies to individuals (including those investing through flow-through entities) and closely-held "C" corporations, but does not apply to broadly held corporations, such as publicly-traded corporations.

The passive activity loss provisions were relaxed in the case of some oil and gas industry investments. There is an exception to the passive activity loss rules for taxpayers otherwise subject to this onerous limitation if the taxpayer acquires a working interest in an oil and gas property. The use of such tax losses, which are prevalent in the start-up phase of many projects, provides a higher after-tax return to the investor. This working interest exception is limited in scope, however, and precludes the use of a limited partnership or limited liability company taxed as a "flow-through" entity. This limitation acts as a *disincentive* to investment to project financing by individuals.

The same generally applicable passive activity loss rules apply to ventures in the biotechnology field. This is one of the major factors in the organization of numerous life sciences projects as "C" corporations, which are taxed at the entity level, rather than tax partnerships or other types of flow-through entities. The passive activity loss rules defer the utilization of tax losses and tax credits for individuals investing through flow-through entities unless the individuals otherwise have passive income. As a result, existing tax incentives such as the Section 41[3] research credit or the Section 174 research and experimental expenditure deduction can be ineffective for individual life sciences investors that do not otherwise have passive income. This imposes a tax drag on returns from start-up investment in the life sciences industry. In contrast to tax partnerships and other flow-through entities, "C" corporations do not flow through losses or credits to the stockholders of the corporation at all. As a result, if the entity does not become profitable or if it is acquired in certain transactions, the tax losses and tax credits may end up expiring unused or otherwise being limited.

There may be non-tax reasons for the use of "C" corporations in the life sciences industry, but the application of the passive activity loss rules (and resultant inability to immediately take advantage of tax benefits at the investor level) is a significant tax reason. A major impact of the enactment of this provision was the move away from the use of research and development limited partnerships ("R&D LPs") that once financed biotechnology investment and played a significant role in the 1980s and 1990s to fund critical research and development projects of some of today's successful biotech companies. Since the introduction of the passive activity loss rules in 1986, R&D LPs were forced to rely more heavily on including other benefits (product royalties and warrants of the biotech company) to provide a more attractive return for investors. This in turn altered the economic sharing of the potential gains and losses from these deals.

This proposal would amend the federal income tax laws to remove or modify tax law restrictions on the use of tax losses and tax credits by investors in flow-through entities that invest in life sciences projects in a manner that encourages investment without reinvigorating tax shelters. A

[3] All "Section" or "§" references are to sections of the Internal Revenue Code of 1986, as amended, unless specified otherwise.

separate proposal would provide tax incentives similar to those available to the oil and gas industry to incentivize investment in the life sciences industry.

Description of Proposal

This proposal would enact amendments that would promote investments by individual taxpayers in the biotechnology industry through non-corporate joint ventures, limited liability companies, limited partnerships, or "S" corporations that conduct biotechnology research. Specifically, the proposal would enact amendments to the Code that would permit a life sciences company's tax benefits (deductions related to research and experimental expenditures, losses from the research and development of a project, and research tax credits) to "flow through" to the individual investor without limitation under the passive activity loss rules. This would result in immediate tax benefits to individual investors and thus attract more investment in small life sciences companies. The exception to the passive activity loss rules would be modeled after the existing exception for working interests in oil and gas properties.

Small Biotechnology Business Definition

Under the proposal, a taxpayer that invests in a flow-through entity that qualifies as a specially-defined "small biotechnology business" would be eligible for an exception to the application of the passive activity loss rules. Such a small biotechnology business would be based on existing Code provisions that are similarly targeted towards small businesses. A small biotechnology business would be defined as: (1) any flow-through entity if the annual average number of employees employed by such person during either of the 2 preceding calendar years was 500 or fewer under Section 41(b)(3)(D)(iii) or (2) any flow-through entity that, if treated as a "C" corporation for federal tax purposes, meets the definition of a qualified small business under Section 1202(d), substituting a $150 million gross asset test (with special rules for taking into account intangible assets of the company). Controlled group rules would apply to ensure that the persons availing themselves of this passive activity loss exception are truly a small biotechnology business.

Qualified Biotechnology Research and Development

In order to be eligible under this proposal, the small biotechnology business must conduct sufficient "qualified biotechnology research and development" to meet a minimum threshold amount.

The research and development prong would build off of the existing Section 41 research credit. Thus, the company's activities would need to meet the "qualified research" definition under Section 41(d)(1)(B). Specifically, the project would need to focus on research activities undertaken for the purpose of discovering information—

- which is technological in nature, and
- the application of which is intended to be useful in the development of a new or improved business component of the taxpayer.

This prong would also incorporate the standards used by the IRS in determining whether there is "qualified research" under Section 41(d) (*e.g.*, uncertainty, related to development/improvement, etc.), with appropriate modifications for purposes of this provision.

The biotechnology portion of the test would provide that the research and development conducted by the company must be in a recognized biotechnological field. This would be defined as a project designed to:

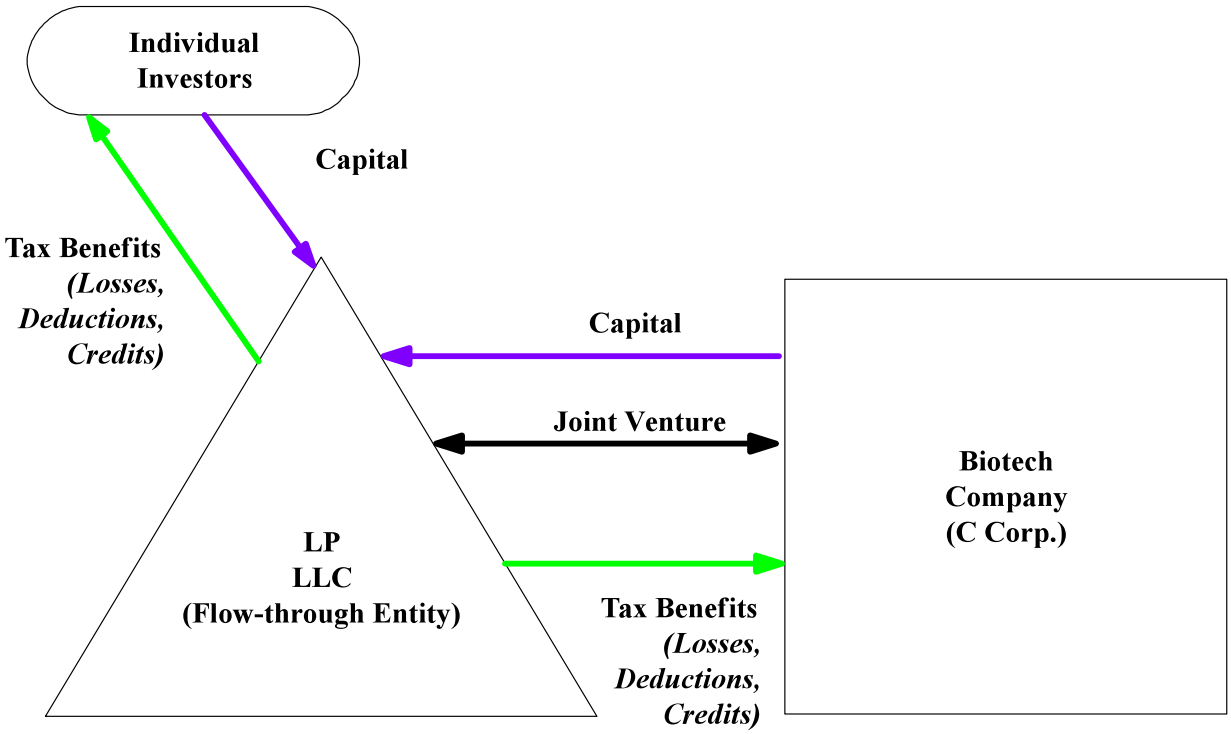
- Treat or prevent diseases or conditions by conducting pre-clinical activities, clinical trials, and clinical studies, or carrying out research protocols, for the purpose of securing FDA approval of a product under section 505(b) of the Federal Food, Drug, and Cosmetic Act or section 351(a) of the Public Health Service Act.
- Diagnose diseases or conditions or to determine molecular factors related to diseases or conditions by developing molecular diagnostics to guide therapeutic decisions.
- Develop a product, process, or technology to further the delivery or administration of therapeutics.
- Develop other projects in the biotechnology industry.

The minimum threshold amount of qualified biotechnology research and development would require that substantially all of the business activity of the company would consist of conducting research and development in the biotechnology field. "Substantially all" would be determined based on appropriate measures that are suitable for research and development small businesses, such as a specified ration of research and development expenditures to product revenues.

Other Considerations

The statutory amendments and relevant legislative history would provide that tax benefits from investments in such projects would not be disallowed under the economic substance doctrine of Section 7701(o) and case law or Section 183 (the hobby loss rules) solely as a result of start-up losses incurred by such businesses. The proposal would also contain aggregation rules based on existing Code provisions that treat separate entities as being under "common control" in order to ensure that taxpayers do not inappropriately set up separate research and development flow-through entities intended to qualify as small biotechnology businesses.

Project Structure Using Flow-through Entity for Biotechnology Investment



SECTION 1202 CAPITAL GAINS REFORM

Present Law

Section 1202 provides a small business investment tax incentive that Congress enacted in 1993.[4] Under Section 1202, non-corporate taxpayers generally may exclude 50% (temporarily increased) of their gain from the sale or exchange of qualified small business ("QSB") stock that has been held for more than 5 years. Special exclusion rates apply to certain empowerment zone businesses.

Section 1202 currently has had a greater theoretical than practical impact on small business investment, including the biotechnology sector. Tax law changes dating back to the mid-1980s have caused many biotech start-ups to organize as "C" corporations. In 1986, Congress enacted the passive activity loss rules of Section 469, which limits individuals and closely-held corporations from offsetting active income (such as wage income) and investment income with losses from passive activities. This change made the use of so-called "R&D limited

[4] All "Section" or "§" references are to sections of the Internal Revenue Code of 1986, as amended, or the Treasury Regulations promulgated there under.

partnerships" and other pass-through entities less attractive to individual investors, who could no longer immediately use the tax losses generated by these projects.

For "C" corporation biotech firms, individual investors are potential candidates for the Section 1202 exclusion. Despite the seemingly favorable tax benefits provided by Section 1202, in practice the provision has never lived up to expectations. This has been due to the complexity of the rules, its limited scope, subsequent changes in tax rates, and the alternative minimum tax ("AMT").

This proposal would simplify Section 1202 in some respects to make it more user-friendly. This is an important consideration given anecdotal reports of high IRS audit rates for taxpayers claiming the exclusion. The QSB stock rules would also be modified to provide an actual tax benefit to investors and expanded to apply to start-up ventures not organized in corporate form (such as limited partnerships and limited liability companies), reflecting the evolution of business entity choice since the enactment of Section 1202.

Qualified Small Business Eligibility

The Section 1202 exclusion applies to QSB stock, which is stock:

- issued by a "C" corporation after August 10, 1993,
- issued by a corporation that is a QSB as of the date of issuance,
- acquired by the taxpayer at original issue, including through an underwriter, in exchange for money or property other than stock or for services (excluding underwriting services),
- the issuer of which is an eligible corporation that meets an active business requirement during substantially all of the taxpayer's holding period for such stock, and
- that is not disqualified as QSB stock on account of specified types of redemptions.

There are multiple requirements for a business to be treated as a QSB under the current rules:

- **"C" Corporation.** A QSB must be a domestic "C" corporation.

- **Active Business Requirement.** In order to meet the active business requirement, at least 80% of the corporation's assets (based on value) must be used in the active conduct of one or more "qualified trades or businesses." Qualified trades or business are any trades or businesses other than specified business engaged in providing services (*e.g.*, health, law and those relying on the reputation or skill of employees), finance, farming, certain natural resource production or extraction, or a lodging or restaurant business. The active trade or business test takes into account assets held by subsidiaries, portfolio investments, working capital, real estate holdings, and computer software royalties. Taxpayers engaged in Section 195 start-up activities, Section 174 research and experimental activities, or Section 41 in-house research activities are treated as using their assets in the active conduct of a qualified trade or business. The active business requirement takes into account factors such as working capital, investment assets and investments in subsidiaries for purposes of the 80% test.

- **Gross Assets Test.** The issuer's gross assets must be $50 million or less both before and immediately after the stock is issued. Although stock can continue to be QSB if the issuer's assets exceed $50 million after the issuance of the stock, once the $50 million

threshold has been exceeded, the corporation will not be permitted to again issue stock that will qualify as QSB stock. The determination of gross assets is generally determined by reference to the amount of cash and the adjusted tax basis of other property. In the case of contributed property, gross assets are determined based on FMV. Modified controlled group rules apply to aggregate parent-subsidiary corporations.

Per-Issuer Limitation
Taxpayers can only exclude a specified amount of gain with respect to the QSB stock of a single issuer. The gain limitation is the greater of:

(1) 10 times the taxpayer's aggregate adjusted tax basis in the QSB stock of that issuer disposed by the taxpayer during the taxable year, or
(2) $10 million (reduced by the aggregate amount of the gain taken into account by the taxpayer under Section 1202 with respect to that issuer in any prior year).

5-Year Holding Period
In order to qualify for the exclusion, the QSB stock must have been held for more than 5 years.

Redemption Rules
Certain redemptions can preclude a purchase of stock from qualifying as a purchase of QSB stock. The rules are more restrictive if there is a "significant redemption" of more than 5% of the QSB's stock (by value) during a specified period.

Miscellaneous Rules
Section 1202 also contains rules addressing stock acquired through the conversion feature of convertible QSB stock, QSB stock held by pass-through entities, certain tax-free and other transfers, basis rules, and short position rules.

Increased Exclusion for QSB Stock Issued in 2009, 2010 and 2011
The American Recovery and Reinvestment Act of 2009 temporarily raised the Section 1202 exclusion from 50% to 75% for QSB stock acquired after February 17, 2009, and before January 1, 2011 (amended as indicated below).

The Small Business Jobs Act of 2010 and the Tax Relief, Unemployment Insurance Reauthorization, and Job Creation Act of 2010 temporarily have provided a 100% exclusion for QSB stock acquired after September 27, 2010, and before January 1, 2012. In addition, the preference item treatment under the AMT for such stock was temporarily eliminated.

Problems with Existing Section 1202

Impact of the Reduction in Capital Gains Tax Rates
At the time of enactment of Section 1202 in 1993, capital gains tax rates were higher. The application of the QSB stock exclusion was (and remains) linked to a 28% tax rate that results in little benefit for sellers of QSB stock (a 14% effective tax rate on the gain). The maximum long-term capital gain rate has since been reduced to 15% (expiring December 31, 2012). As a result, the effective tax rate for QSB after application of the exclusion remains 14%, so there is a mere

1% difference from otherwise applicable long-term capital gain tax rates. This 1% difference hardly acts as an incentive for a taxpayer to hold QSB stock for 5 years, when a 15% long-term capital gains tax rate is otherwise available after one year.

Impact of the Alternative Minimum Tax
The AMT reduces the benefit of the Section 1202 exclusion because a portion of the QSB gain is treated as a preference item. The add-back of this preference item (7% of the excluded gain) can result in the taxpayer paying a higher effective tax rate, although this tax preference has temporarily been eliminated for certain investments.[5] Another issue that arises under the AMT is that Section 1202 is mandatory, so if the taxpayer is not benefitted under this provision on account of the AMT, then the taxpayer must deliberately fail to qualify for the provision.

Valuation and Measurement Issues.
The qualified trade or business requirement necessitates both valuations and monitoring for compliance/record-keeping in connection with the "substantially all" requirement throughout the 5 year holding period. For example, the QSB must monitor its "reasonably expected" research and experimental expenditures and working capital needs in connection with holding investment assets for compliance with the substantially all test. Similarly, the gross assets test can require difficult valuation issues and record-keeping issues that can be especially problematic with intellectual property and follow-on investments.

Cap on Excluded Gains of a Single Issuer.
The per-issuer cap can work counter to the stated purpose of incentivizing investment in small businesses. Many taxpayers invest in numerous projects, a large portion of which do not pan out. Large gains from a successful project or projects are hoped to offset losses from other small business projects, plus provide a significant return (the "home run" scenario). The cap on the amount of gain able to be excluded undermines the benefits of having a large gain from a winning investment.

Holding Period for QSB.
The 5-year holding period can be problematic because it is lengthy, especially given the historically minimal benefit of Section 1202. Moreover, it can be problematic for follow-on financings, because later-stage investors may not be able to satisfy the holding period requirement by the time of a liquidity event.

C Corporation Requirement for QSB.
The "C" corporation requirement excludes "S" corporations and pass-through entities (such as partnerships and limited liability companies that have not elected to be taxed as "C" corporations).

Non-corporate Investor Requirement.

[5] Other examples of where AMT rules were eliminated temporarily or permanently include the specified credit rules of Section 38(c)(4) for specified credits, such as the Section 45 refined coal credit and Section 40 alcohol fuels credit.

Corporate taxpayers, which do not enjoy preferential long-term capital gains tax rates, cannot benefit from the Section 1202 exclusion.

Miscellaneous Provisions

The testing period for assets held for investment that are reasonably expected to be needed in the next two years for research and experimental expenditures or increased working capital limits the amount of investment assets that the QSB can hold and imposes a monitoring requirement on taxpayers.

The "significant redemption" rules may cause some equity investments in the QSB to not be eligible for QSB stock treatment, even if such redemption had a business purpose and was not intended to avoid the rules of Section 1202.

Description of Proposal

Congress's original intent in enacting Section 1202 was to encourage and reward individuals for taking risks by investing in new ventures and small businesses. This laudable policy goal continues to thrive today. Along the same lines, the Obama Administration's 2012 budget proposal included a permanent extension of the 100% exclusion of gains on QSB stock. While the congressional intent of Section 1202 and the Administration's proposal are intended to spur job creation and economic growth through new investments in small businesses stocks, the current Section 1202 requirements unfortunately are overly complex and do not provide adequate incentives to invest in small companies.

The application of the QSB exclusion to many small companies is hindered by the complexity, administrative cost, uncertainty, and out-dated parameters of the current rules. The simplification of existing Section 1202 and expansion of its exclusion to adapt it to current business entity choice practices would provide the platform to carry out the congressional intent to increase investment in small companies.

Proposed Amendments to Section 1202

1. Implementation of a graduated series of exclusions for QSB stock (or, as described below, equity interests in other types of entities) based on the taxpayer's holding period for the stock. The exclusions would be:
   - 50% for QSB stock held for more than one year but not more than three years.
   - 75% for QSB stock held for at least three years, but not more than 5 years.
   - 100% for QSB stock held for more than 5 years.
2. Repeal the AMT preference.
3. Increase the aggregate gross asset test for a "qualified small business" from $50 million to $150 million, indexed to inflation, and simplify the active business requirement to apply based on a Section 162 trade or business standard.
   - Also, other helpful revisions would include allowing increased assets from follow-on rounds of financings to not automatically be included for purposes of the gross assets test and excluding intellectual property/intangibles from the gross assets test.
4. Eliminate the per-issuer limitation or increase it to $20 million per QSB.
5. Permit "S" corporations and non-corporate entities to qualify as QSBs, subject to appropriate limitations such as controlled group rules.

6. Allow corporations (and not just individuals) to take advantage of the gain exclusion for QSB stock.
7. Modify the significant redemption rules that apply to determine whether stock is QSB stock by providing that a purchase with a business purpose shall be disregarded if one of the principal purposes was not the avoidance of limitations in Section 1202.
8. Modify the rules for determining when working capital is taken into account for purposes of the active business test by treating investment assets reasonably expected to be used within 5 years to finance research and experimental activities in a qualified trade or business or increases in working capital needs of a qualified trade or business.
9. Delink the Section 1202 exclusion from the 28% tax rate that currently applies
10. Clarify that biotech is a qualified trade or business.

Comparison of Existing Law and Section 1202 Proposal

In its current form, Section 1202 is too complex and has failed to track recent developments in both the tax laws and in entity choice for small businesses. Thus, Section 1202 is little-used by small business investors. In order for Section 1202 to achieve its stated goals of encouraging investment in small businesses, a number of revisions are needed. The impact of such changes would be increased investment by venture capitalists and other investors in the biotechnology industry, among other sectors of the economy. Below is a side-by-side comparison of existing law and the proposed revisions to Section 1202, along with supporting reasons for each of the amendments.

	Current Law	Proposed Modification/Rationale
Gain Exclusion and Holding Period	Taxpayers generally may exclude up to 50% of the gain from the sale of QSB stock held for more than 5 years. Under ARRA, the exclusion was temporarily increased to 75% for stock acquired after 2/17/09 and before 1/1/11 (modified by subsequent legislation) Under the Small Business Jobs Act of 2010 and the Tax Relief, Unemployment Insurance Reauthorization, and Job Creation Act of 2010, the exclusion was temporarily increased to 100% for stock acquired after 9/27/10 and before 1/1/12.	Support graduated exclusion rates based on the taxpayer's holding period for the QSB stock. *Rationale-While a 50% ex-clusion of gain from the sale of QSB stock can incentivize investors, such exclusion should be available to investors not holding QSB for substantial period of time. A 75% ex-clusion (3-5 year holding period) and a 100% exclusion (5 year + holding period) would likely increase the inflow of investment, particularly to higher-risk innovative small business such as biotech, clean tech, and high tech.
AMT Preference	A percentage of the excluded gain is a preference under the AMT,	Support the permanent elimination of the AMT preference item for

	Current Law	Proposed Modification/Rationale
	subject to the temporary elimination of this rule.	gain excluded. *Rationale-The AMT preference reduces the existing Section 1202 tax benefits. By eliminating the AMT preference, investors would be able to fully benefit from Section 1202.
Aggregate Gross Assets Test and Active Trade or Business	The issuer of stock must meet a $50 million gross assets test and apply complicated rules to determine whether there is an active trade or business.	Support raising the gross asset test to $150M in gross assets and exclude intellectual property/intangibles for purposes of the test. Related changes would permit maintenance of QSB stock status for newly-issued stock in follow-on rounds of investments. *Rationale-The use of a gross assets test to define "small businesses" that qualify for Section 1202 limits innovative small businesses that become ineligible for the QSB exclusion for later investors due to their continuous need for private financing coupled with high value intellectual property. Thus, innovative small businesses, while small in terms of operations (*i.e.*, employee size, product revenue) are penalized for their intellectual property and ability to raise much-needed scarce private capital. Simplify the active trade or business test by applying a Section 162 standard. *Rationale-Eliminating the complex active trade or business test would simplify compliance and avoid difficult valuation and monitoring issues.
Per-Issuer Limitation	The maximum amount of gain eligible for the exclusion by a taxpayer for any corporation	Support elimination of the per issuer limitation or an increase in the limitation to $20 million.

	Current Law	Proposed Modification/Rationale
	during any year is the greater of: (1) 10X the taxpayer's basis in stock issued by the corporation and disposed of during the year, or (2) $10M reduced by gain excluded in prior years on dispositions of the corporation's stock.	*Rationale-Given the long lead time and substantial financing needed to bring a therapy to market, a cap on the exclusion that an investor can receive from an emerging biotech company deters investment of further additional private capital into the company. Thus, by eliminating the per-issuer limitation/cap, an investor will have all of their gains be eligible for the exclusion, which will likely spur additional rounds of financing by existing investors.
C Corporations	A QSB must be a corporate entity.	Support expanding the QSB rules to non-corporate entities. Rationale-Many more businesses organize today as non-corporate entities. The amendment would attract greater investment to small businesses.
Non-corporate Investors	Only non-corporate investors can use the Section 1202 exclusion.	Support expanding Section 1202 to corporate investors. Rationale-This would attract greater investment to small businesses by larger companies who are in the same industry and work on a collaborative manner.
Redemptions	Significant redemptions are taken into account for purposes of determining whether stock issued is QSB stock.	Support disregarding any purchase that has a business purpose provided that one of the principal purposes was not the avoidance of limitations in Section 1202. Rationale-Redemptions that meet such a test do not present an abusive situation and will promote increased investment in QSB's because potential investors will now not be trapped by an unfair technical rule that would otherwise apply.
Working Capital	Investment assets may only be	Support permitting companies to

	Current Law	Proposed Modification/Rationale
	taken into account for purposes of the active business test if such assets are reasonably expected to be used within two years for research and experimental purposes or increased working capital needs.	take investment assets into account if reasonably expected to be used within 5 years for research and experimental purposes or increased working capital needs. Rationale-This will provide greater flexibility for QSB's to use funds in their business without running afoul of the active business test and permit QSB's to expend such funds in due course without the threat of failing to qualify as a QSB.
28% Rate Subject to Exclusion	The Section 1202 exclusion (ranging from 50% to 100%) applies to a base 28% tax rate, resulting in an effective tax rate ranging from 14% to 0%.	Delink the Section 1202 exclusion from the base 28% rate and apply it to the long-term capital gains tax rate. Rationale-At the time of enactment, there were higher capital gains rates and the 28% base rate provided an incentive for the Section 1202 exclusion as compared to the long-term capital gains rate. Lower capital gains tax rates have reduced the spread between the Section 1202 exclusion (apart from the recent tax acts providing for a 100% exclusion) and long-term capital gains tax rates. By applying the Section 1202 exclusion to the long-term capital gains tax rate, investors in QSB's will have a true incentive to qualify for this tax benefit, which will promote investment in such entities.
Qualified Trade or Business	Certain businesses are excluded from the definition of a qualified trade or business, including those in the field of health where the principal asset is the reputation or skill of one or more of the	Support clarification that biotech is not excluded from the definition if a qualified trade or business, even if the reputation or skill of an employee is a principal asset at the outset of the business.

	Current Law	Proposed Modification/Rationale
	employees.	Rationale-This clarifies that life sciences are not the type of trade or business intended to be excluded.

SMALL BUSINESS EARLY-STAGE INVESTMENT PROGRAM

Background

Bringing groundbreaking therapeutics from bench to bedside is a long and arduous road, and small biotechnology companies are at the forefront of the effort. It takes an estimated 8 to 12 years for one of these breakthrough companies to bring a new therapy from discovery through Phase I, Phase II, and Phase III clinical trials and on to FDA approval of a product. The entire endeavor costs between $800 million and $1.2 billion. However, the current economic climate has made private investment dollars extremely elusive.

As U.S. biotech companies face financial uncertainty, other countries are increasing their investments and considering intellectual property protections to encourage domestic biotech growth. As part of its efforts to develop a world class biotech industry, the Chinese government is implementing a 5-year plan (2006-2010) in which it promotes agricultural biotechnology, builds demonstration projects for the commercial production of vaccines and gene-modified medicines, and enhances the capabilities for new medicine development and production. India is in the process of laying out its National Biotechnology Regulatory Authority. Among the initiative's goals is to encourage early-stage innovation, technology transfer, and startup formation. Up to 30% of the government's biotech budget will be invested in public-private partnership programs designed to promote innovation, pre-proof-of-concept research, accelerated technology, and product development.

While grant programs such as SBIR have proven helpful to the industry, more needs to be done to ensure the U.S. biotech industry's prosperity for years to come. In 2010, venture capital fundraising endured its fourth straight year of decline and its worst since 2003. Biotechnology received just $2 billion in venture funds, a 27 percent drop from its share in 2009. Even worse, the biggest fall was seen in initial venture rounds, which are the most critical for early-stage companies. Series A deals last year brought in just over half of what they did in 2009. Incorporating an early-stage venture capital matching program would provide a capital infusion for the beginning stages of therapeutic projects.

Proposal

The "Small Business Early-Stage Investment Program" would provide $1 billion in grants for venture capital investments in certain industries, including life sciences. Under the program, the SBA's investments would be treated the same as investments by other limited partners in an investment fund, except that the SBA would not receive any control or voting rights with respect to the early-stage small business. Importantly, the new program protects the interest of the taxpayer by specifying that grants could only be awarded to investment companies that had

already raised an equivalent amount of capital from private-sector sources. Ideally, over time, the SBA's investment program will become self-sustaining as funds from successful small businesses are repaid into a revolving fund.

Investment Company Criteria:

- In order to participate, an investment company (incorporated body, LLC, or limited partnership) must submit a business plan describing its investment strategy in early-stage and small business concerns in targeted industries or other business sectors, information about the expertise of the management team, and as the likelihood of success and profitability.

- Targeted businesses include the following: agriculture technology; energy technology; environmental technology; life sciences; information technology; digital media; clean technology; defense technology; and photonics technology.

- A participating investment company must make all of its investments in small business concerns, 50% of which must be early-stage small businesses. The definition of an early-stage small business requires that it is a U.S. small business concern and has less than $15 million in gross annual sales revenues for the previous 3 years.

Investment Company Application Process:

- The SBA must make conditional approvals or disapprovals of applications within 90 days of receiving the application. If an investment company has met all of SBA conditions final approval will be given 30 days after the date SBA has determined all conditions have been met.

- If there are areas that need to be addressed in order to receive final approval the investment company will have a year to satisfy conditions for final approval. Final approval of the applications will be made within 90 days after the date the applicant has met all approval conditions. If conditions are not met within the time period the application will not be able to participate in the program.

Equity Financing:

- The SBA will commit equity financing to an investment firm that can be drawn upon to make new investments for 5 years from the date of the first draw, and make follow-on investments and management fees for 10 years from the date of the first draw.

- The SBA will not provide equity financing that is greater than the amount of non-federal capital (on or before date when equity financing is used) and no single investment company can receive more than $100 million.

Investment Shares & Equity Financing Interest:

- Each investment made by the investment company shall be treated as comprised of capital from equity financings under the program according to the ratio that capital from the program bears to all capital available to the investment company for investment.

- Equity financing interest conveyed to the SBA has the same rights of other investors (receives distributions in the same time and in the same amount as other investors) in regards to interests but does not denote control or voting rights to the SBA.

- The SBA is entitled to a pro rata portion of any distributions made equal to the percentage of capital in the investment company the equity financing comprises.

- Manager profits interest cannot exceed 20 percent of the profits (exclusive of any profits that may accrue as a result of capital contributions of managers). No manager profits interest (other than a tax distribution) shall be paid prior to the repayment to investors and the SBA.

SMALL BUSINESS TAX INCENTIVES

SECTION 382 NOL REFORM

Present Law

General

A "C" corporation may generally carry forward its unused net operating losses ("NOLs") to future years and use these NOLs to offset its future taxable income. Section 382 was enacted to limit tax-motivated acquisitions of corporations with NOLs, built-in losses, and other tax attributes eligible to be carried forward (referred to as a "loss corporation").[6] Section 383 similarly applies to loss corporations with tax credits, capital loss carry-forwards, and other tax attributes.

Section 382 plays a significant role in limiting the use of tax attributes in the high tech industry. Many high tech start-up companies (including biotech start-ups) are organized as "C" corporations for a variety of reasons (including an individual investor's inability to use losses flowing through a tax partnership or "S" corporation on account of the passive activity loss rules, desire to issue stock options, non-tax preferences for more well-developed corporate law, etc.). These high tech companies are involved in capital intensive research and development that involves a significant lag time (up to a decade or more) for the commercialization of their products. On account of their expenditures being deductible (including immediately under Section 174, unless 5-year or greater amortization is elected), depreciable or amortizable, these "C" corporations can generate significant losses in their early years. The financing of these early-stage ventures is typically through multiple stage equity financings, as the companies grow and can attract the attention of angel investors and then venture capitalists. This multi-stage equity financing can and does result in significant restrictions on the ability of these companies to use their tax losses. This is because increases in the ownership of the company on account of, *e.g.*, new investors purchasing stock, may cause an "ownership change" for purposes of Section

[6] All "Section" or "§" references are to sections of the Internal Revenue Code of 1986, as amended, or the Treasury Regulations promulgated there under.

382. This ownership change may limit a high tech company's ability to use its losses to offset income that is ultimately generated from the commercialization of the research and development.

Operation of Section 382
In general, Section 382 operates by limiting the amount of taxable income that a loss corporation may offset with NOLs, built-in losses, and other tax attributes that arise before an "ownership change." Such limitation is determined by multiplying the value of the stock of the loss corporation immediately before the ownership change by a specified interest rate.

Ownership Change
For purposes of Section 382, an ownership change occurs when there is an increase of more than 50 percentage points in stock ownership of a loss corporation by one or more "5-percent shareholders" during the testing period (generally, a 3-year period ending on the date on which a transaction is tested for an ownership change). The determination of whether an ownership change has occurred is made after any owner shift involving a 5-percent shareholder or any equity structure shift (generally, tax-free reorganizations or mergers).

5-percent Shareholder
A 5-percent shareholder generally includes any individual who directly or indirectly owns 5-percent or more of the loss corporation during the testing period, and public groups of individuals, entities or other persons, each of whom directly or constructively owns less than 5-percent of the loss corporation, but whose ownership is aggregated together as a 5-percent shareholder.

Owner Shift Involving a 5-percent Shareholder
An owner shift involving a 5-percent shareholder is any change in the respective ownership of stock of a corporation that affects the percentage of stock held by any person who is a 5-percent shareholder before or after such change. An owner shift involving a 5-percent shareholder includes, but is not limited to, the following types of transactions:

(1) A taxable purchase of loss corporation stock by a person who is a 5-percent shareholder before the purchase;
(2) A disposition of stock by a person who is a 5-percent shareholder either before or after the disposition;
(3) A taxable purchase of loss corporation stock by a person who becomes a 5-percent shareholder as a result of the purchase;
(4) An exchange of property for stock in a Section 351 transaction that affects the percentage of stock ownership of a loss corporation by one or more 5-percent shareholders;
(5) A redemption or recapitalization that affects the percentage of stock ownership of a loss corporation by one or more 5-percent shareholders; and
(6) An issuance of loss corporation stock that affects the percentage of stock ownership of a loss corporation by one or more 5-percent shareholders.

Equity Structure Shift
An equity structure shift is generally includes tax-free reorganizations under Section 368 (with a few exceptions for special types of tax-free reorganizations, including those involving bankrupt corporations), public offerings and taxable mergers.

> **Example.** An acquiring corporation and a target loss corporation without any overlapping ownership combine in a taxable merger in which the target's shareholders receive mostly cash and some acquiring corporation stock. The acquiring corporation is the survivor of the merger. Following this equity structure shift, an ownership change would occur if the shareholders of the target loss corporation do not own at least 50% of the stock of the acquiring corporation immediately after the merger. If the shareholders of the target loss corporation receive less than 50% of the acquiring corporation's stock, the original shareholders of the acquiring corporation would have increased their ownership interest in the target loss corporation by more than 50 percentage points (*i.e.*, 0% ownership immediately before the transaction and more than 50% ownership interest immediately after).

Proposals
Congress's original intent in enacting Section 382 was to prevent the trafficking of NOLs and other tax attributes - *e.g.* profitable companies buying loss corporations in order to acquire their NOLs to offset taxable income. Unfortunately, the law as written is overly broad and fails to recognize that certain corporations, such as high tech start-up companies, often rely on raising equity through successive financing rounds to successfully negotiate a long product development process. The following proposals are limited exceptions that maintain the underlying rationale for Section 382 – preventing abusive trafficking of NOLs and other tax attributes – while providing high tech corporations with the ability to raise needed capital through multiple stock issuances and to combine the research and development operations of multiple high tech corporations, without incurring an unnecessary tax penalty. These proposals are set forth as alternatives below.

Description of First Proposal: Section 174 Expenditures
Under the first proposal, in the event of a Section 382 ownership change, the portion of any net operating loss or net unrealized built in loss attributable to research and experimental expenditures under Section 174 paid or incurred when the corporation was a "qualified small business corporation" and the portion of that corporation's federal income tax credits generated by research and development under Section 41 would not be subject to limitation under Section 382 or Section 383, respectively.

Qualified Small Business Corporation
Corporations eligible for this provision would include any domestic corporation that is not in bankruptcy and that meets the definition of a qualified small business under Section 1202(d), substituting a $150 million gross asset test (with special rules for taking into account intangible assets of the company).

COBE
The continuity of business enterprise or "COBE" test of Section 382(c) would apply. Under the COBE test, the qualified small business corporation must continue its business enterprise at all times during the two year period following the ownership change.

Description of Second Proposal: Qualified Investments
Under the second proposal, a Section 382 ownership change would not be triggered by: (1) a qualified investment in a qualified start-up corporation or (2) such other transactions involving mergers and acquisitions involving qualified start-up corporations as provided in Treasury Regulations. It would be expected that the Treasury Regulations would provide that the merger of two loss qualified start-up corporations would be eligible for this Section 382 exception.

Qualified Investment
A qualified investment in stock of certain loss corporations that results in an owner shift involving a 5-percent shareholder would be treated as occurring outside of the three-year testing period under the following circumstances.

- The loss corporation must be a qualified start-up corporation.
- The stock must be acquired at its original issuance (directly or through an underwriter).
- The stock must be acquired solely for cash.
- The 5-percent shareholder must not own (directly, indirectly or constructively after the acquisition) 50% or more of the loss qualified start-up corporation.

For purposes of this rule, stock issued in exchange for convertible debt would be treated as stock acquired by the debt holder at its original issuance for cash if the debt was acquired at its original issuance and solely in exchange for cash.

Qualified Transaction
A qualified transaction means any merger or acquisition involving two qualified start-up corporations that results in an owner shift or an equity shift to the extent provided in Treasury Regulations.

Qualified Start-Up Corporation
A qualified start-up corporation is a corporation that (A) has an average annual number of employees during either of the two preceding years that was 500 or fewer under Section 41(b)(3)(D)(iii) or (B) meets the definition of a qualified small business under Section 1202(d), substituting a $150 million gross asset test (with special rules for taking into account intangible assets of the company). A qualified start-up corporation must meet the COBE test and an expenditure test.

COBE Test
The qualified start-up corporation must meets the COBE test described above.

Expenditure Test

Under the expenditure test, the qualified start-up corporation must have at least 35% of its expenditures in a taxable year (taking into account redemption payments) be for research and development expenditures described in Section 41(b) and/or research and experimental expenditures described in Section 174. The expenditure test would apply for a measuring period that includes the taxable year in which the closing of the stock issuance occurs and the two preceding taxable years.

Redemptions, Qualified Investment Groups, and Other Rules

There would be rules similar to those applied to redemptions under the Section 1202 qualified small business stock provision for redemptions of stock in a qualified start-up corporation for purposes of determining whether an investment is a qualified investment.

Unless specified in regulations to be published by the Treasury Department addressing customary transactions in the high technology industry, transactions occurring between a qualified start-up corporation and a member of its "qualified investment group" may disqualify what would otherwise be a qualified investment. A presumption against a qualified investment would apply if the qualified start-up corporation received, in a transaction taking place during the two year period beginning one year before any qualified investment, any consideration other than cash. A qualified investment group with respect to a qualified investment means one or more persons who receive stock in exchange for the qualified investment and persons related thereto applying Section 267(b) or Section 707(b).

Treasury regulations would also be authorized to address abusive transactions and the application of similar rules to this provision for Section 383 (concerning similar limitation on tax credits and other tax attributes) and Section 384 (concerning use of pre-acquisition losses to offset built in gains of acquiring corporations.

Other necessary rules and regulations (*e.g.*, exemption from the separate return limitation year rules that can be applicable to consolidated group members) would also be provided for transactions under Treasury Regulations to be issued.

AMT

The alternative minimum tax net operating loss rules would be revised for qualified start-up corporations to remove the current AMT NOL restrictions.

INCENTIVES FOR NON-INVESTOR CAPITAL

REPATRIATION

Present Law

Overseas earnings of U.S. companies are currently taxed at 35 percent when they are repatriated back to the United States. In 2004, Congress passed the American Jobs Creation Act in an effort to create jobs and boost the economy. This legislation contained a repatriation provision granting U.S. multinational corporations a one-time tax break on money earned in foreign countries.

The tax break allowed foreign earnings to be taxed at a rate of 5.25%, which is significantly lower than the corporate tax rate of 35%. Previously, much of the earnings derived from foreign countries were not transferred back to the U.S. because multinationals can defer paying taxes on foreign earnings until such earnings are repatriated to the U.S. in the form of a dividend.

Ultimately, Congress's rationale was that the tax break would act as a strong incentive for American multinationals to send their foreign earnings back to the U.S. and then use the earnings to create more American jobs and/or expand operations in the U.S.

Critics of repatriation believe that because the companies were not required to use the repatriated earnings for the sole purpose of American job creation, there was no guarantee that the tax break would increase job creation. Companies were, however, barred from using the money for executive compensation, dividends, and stock investments. Furthermore, the tax break was seen by critics as a reward for companies that deferred regular repatriation of foreign earnings and a punishment for companies that regularly send money back. Critics worried that the act would set a bad precedent, as U.S. multinationals could view the tax break as an incentive to withhold future foreign earnings in the hope that another repatriated tax break would occur.

Description of Proposal

This proposal would allow a taxpayer to return foreign earnings at a tax rate of 5.25%, provided that the returned funds are used in the United States to advance activities as they relate to IRC Section 41(d). Examples may include but are not limited to:

1) Hiring scientists, researchers, and comparable personnel engaged in research and development.
2) Making new investments in research and development projects or facilities.
3) Conducting research related to a new or improved function, performance, reliability, or quality.

The returned funds would be required to be kept in a separate account from the rest of the taxpayer's finances, and could only be withdrawn for permitted activities. Companies would have to invest in U.S. research and development in the same tax year that they file for the reduced rate.

The taxpayer would have the burden of proving to the Internal Revenue Service (IRS) that its returned funds were used solely and specifically for activities associated with Section 41(d). The election to return certain foreign earnings for qualified use is limited to the first 2 years following enactment.

Analysis

The proposal could make the U.S. more competitive with other countries that have lower corporate tax rates.

This proposal directly incentivizes U.S. research and development by tagging activity to Section 41(d). One of the critiques of other repatriation proposals is that companies would bring funds

back to the U.S. to enjoy the tax break, but would be unwilling to expend the funds into the U.S. economy during a recession. This proposal requires that taxpayers invest the money immediately into the economy to take advantage of the reduced rate. Additionally, the proposal would bring some additional revenues to the U.S. Treasury because there would be some tax paid on it which is not being paid today. The proposal would make the U.S. competitive with other countries that have lower tax rates. Supporters of similar repatriation proposals cite international tax laws — as well as the U.S.'s extremely high corporate tax rate — as making the U.S. less competitive and hindering economic growth and job creation. Supporters of repatriation proposals credit the 2004 repatriation law for helping to return roughly $300 billion in overseas income.

Lawmakers in both parties are looking for fiscal remedies, and this proposal aims to bring funds that would otherwise remain abroad back to be reinvested into the U.S. economy.
Politically, the return of Republican control in the House and persistently high unemployment have tech leaders and coalitions hopeful that lawmakers will see a repatriation proposal as a worthwhile fiscal remedy, even amid split party control of Washington. Also, there appears to be some bipartisan support as long as funds returned are immediately invested into the U.S. economy.

Given the current deficit, repatriation could have significant costs.
The Joint Committee on Taxation (JCT) would score the proposal as a tax cut, meaning that it would have a significant cost associated with it.

Repatriation without conditions could be viewed as only beneficial to large multinational corporations. Bipartisan support could exist for a repatriation proposal with conditions, but the types of conditions that will attract support remain unclear.
Politically, repatriation is seen by its detractors as a tax cut for profitable multinational companies that does little to spur growth for smaller companies. With the Senate still controlled by Democrats, it will be unlikely to pass a repatriation bill with no strings attached. It is unclear whether this proposal's requirement of direct investment into the economy will be enough to pass the Senate. Additionally, there is a call from both sides of the aisle to simplify the tax code in upcoming tax reform legislation. With the creation of a special account and the burden to prove to the IRS investment into R&D, it could be argued that this proposal would further complicate the tax code, albeit for a limited amount of time.

Outstanding Issues

1. A repatriation bill limited to the life sciences industry is anticipated to be introduced by Senator Casey and Congresswomen Schwartz. It is a bill that will have a cap of $150M and a 5 year window for the repatriated funds to be used. These conditions would be helpful to mid-size companies rather than large pharmas, which do more collaborations with small biotechs. Is eliminating the cap on the amount of funds that could be brought back, widening the available uses of the funds, and shortening the time horizon to reinvest money a worthwhile approach?

2. The requirement that repatriated funds be used for R&D may be viewed as too strict.

3. Since the repatriation proposal would tag to the current R&D credit, the limitations on contract research may significantly reduce the amount of repatriated funds that a pharma would use in collaborations with small biotechs.

U.S. INNOVATION BOX

Present Law

Currently, the top corporate tax rate in the United States is 35%. In the absence of other tax credits, deductions, etc., this rate is applicable to the entirety of a corporation's taxable income, including capital gains.

Innovation box (or patent box) regimes have been implemented in various forms during the last decade by several countries in Western Europe. These countries, which include Ireland, Luxembourg, Belgium, Spain, France, and the United Kingdom, were attempting to stimulate innovation and job growth within their borders. However, European Union laws regarding freedom of labor movement prevent these countries from requiring that companies participating in the innovation box actually conduct research and create jobs in the country implementing the rate. The U.S. does not face similar restrictions; thus, a U.S. innovation box would more clearly have an employment impact.

Proposed Innovation Box Regime

An innovation box regime would reduce the corporate tax rate on income derived from certain qualifying intellectual property (IP). Any income stemming from the qualifying IP would be taxed at the lower innovation box tax rate, while the remainder of a corporation's income would be taxed at the regular corporate rate of 35%.

The purpose of an innovation box is to attract the employment and economic activity associated with the development and commercialization of certain types of IP, thus fostering innovation and creating jobs through research and development (R&D).

Qualifying IP

Under this proposal, "qualifying" IP would be defined as a patent registered with the U.S. Patent Office. Additionally:

1. All research and development must be conducted in the United States. This includes the original research that leads to the patent application, development between patent application and receiving patent certification from the Patent Office, and further development between certification and the final product.
2. The research must meet the standards of "qualified research" as defined by Section 41(d) of the Internal Revenue Code.

Manufacturing

If the income stemming from the qualifying patent derives from the sale of a product, the manufacturing of that product must take place in the United States for the income to be eligible for the reduced tax rate.

Self-developed vs. acquired IP
Companies would be able to receive a reduced rate for self-developed or acquired IP. For example, if a large pharmaceutical company acquires the rights to a patent in a collaboration with a small biotech company, the income derived from that patent would be eligible for the reduced rate, providing that the acquired IP was developed in accordance with Section 41(d).

The income that the small biotech company gains from the collaboration (upfront payment, milestone payments, etc.) would also be eligible.

If a company markets its self-developed patent on its own, that income would also be eligible.

New vs. existing IP
The reduced tax rate would apply to patents applied for after the date of enactment of an innovation box regime.

Innovation box tax rate
Income derived from qualifying IP would be taxed at a rate of 10%. This rate would remain constant for all income derived from all qualifying patents.

This rate is similar to other western nations that have enacted an innovation box regime. Most recently, the United Kingdom, which has an innovation environment similar to that of the United States, proposed an innovation box with a 10% rate.

Note: This rate represents a negotiable starting point. Other proposed rates in this range would have a similar effect on innovation, research & development, and job creation.

Compatibility with other tax incentives
Participation in the innovation box regime would be elective. If a company elected to take the innovation box rate on the income derived from a given patent, it would not be eligible for any other deductions or credits for the activities that led to that patent or the income stemming from it. However, if a company elected the innovation box rate for one patent and not for another, it would be able to claim credits/deductions for which the latter patent's activities were eligible.

Innovation box election would have to be made in the tax year that R&D began on a project.

Companies could choose not to participate in the innovation box regime and would therefore remain eligible for the current array of other tax incentives.

Cap on eligible income
There would be no cap on the amount of income eligible for the reduced rate. Any income stemming from qualifying IP would be taxed at 10%.

Note: Capping eligible income would be a way to reduce the cost of the regime while retaining the general incentive structure. This cap could be a certain dollar amount or could be a multiple of the cost of developing the patent. In Europe, some countries with a sliding rate scale have implemented a cap on the amount of income eligible for the lowest tax rate (often 0%).

Analysis

A U.S. innovation box regime would incentivize increased R&D and manufacturing jobs in the U.S. and potentially foster collaborations between pharma and small biotechs.

An innovation box regime would have a direct positive effect on R&D jobs in the United States. The possibility of increased profits would incentivize increased investment in R&D, thus creating jobs in both research and manufacturing. Additionally, companies making larger profits would have more funds available to reinvest in new R&D.

Though the confines of Section 41(d) are broader than just biopharmaceuticals, it would incentivize investment in that sector and lead to more innovation and research into potential cures.

The provision allowing the reduced rate even on acquired IP would incentivize collaborations between large pharmaceutical companies looking for preferred tax treatment and small biotech companies conducting qualifying research. A lower tax rate on income related to the collaboration should make the economics of the collaboration more attractive to both parties.

A U.S. innovation box regime would make America competitive as other countries implement new innovation box regimes to boost their research-intensive economies.

The reduced corporate rate would make the United States more competitive on the global stage as companies decide where to locate their research and manufacturing. In the United Kingdom, GlaxoSmithKline recently announced several new domestic projects as a result of the new innovation box regime.

Under a U.S. innovation box, pharma would receive the most immediate benefits since small companies are years away from revenues.

The potential benefits for small companies (i.e. increased collaborations with large pharmaceuticals) are indirect, while the benefits for large companies would be more immediate.

Outstanding Issues

1. Should "qualified research" be defined as Section 41(d) or Section 41? Specifically, many biotech companies use CROs to conduct multi-country clinical trials. Would these activities abroad be considered "qualified research" given that an innovation box is designed to increase domestic R&D? Under IRC Section 41(d)(4)(F), "any research conducted outside the United States, the Commonwealth of Puerto Rico, or any possession of the United States" does not qualify for the R&D tax credit. Is there a way we can allow these sorts of trials – perhaps by citing a different section of the code which is focused on research but allows for

activities done abroad? Another option is to have a new definition for "qualified research" to allow for research that has to be done abroad (i.e., patient population not in existence in U.S.) while putting a limit on the amount of research done out of the U.S. (i.e., less than 50% of activities are done abroad).

2. If applying the innovation box to only new IP, molecules/drugs/products already in the development process would not be eligible. The purpose of the innovation box is to stimulate *new* R&D, innovation, and jobs; it does not make sense to make the reduced rate retroactive. However, one option would be to apply the reduced tax rate to only patents applied for after a certain date (e.g., January 1, 2000) in order to take into account the long development period for biotech. What would be the appropriate date in that scenario? Should there be a phase in for drugs retroactively? A phase in could be very complicated to administer.

3. Would a company's revenues generated outside the U.S. be taxed at the lower innovation box rate?

SECTION 197 AMORTIZATION REFORM

Background

Earlier stage high tech and other research-intensive companies may receive investments from strategic acquirers – venture capital firms established by companies primarily involved in businesses other than investing – that are interested in a commercial relationship with the high tech company. These strategic investors typically have a complementary business that can benefit from license, supplier or service provider arrangements with the high tech company. Strategic investors can also offer assistance in the growth of the high tech company by providing advice and referrals. Investors may also desire to directly acquire the business of the high tech company for commercial reasons. For example, smaller high tech companies often conduct cutting edge research and experimentation that can ultimately benefit more established industry players. Such strategic acquisitions are very important in the biotechnology industry in particular.

Business acquirers often prefer to purchase the assets of a company, for both non-tax and tax reasons. Non-tax reasons include that an asset purchase permits the acquirer to pick and choose the liabilities that are assumed. There are also tax reasons for the purchase of assets, including a step-up in the tax basis of appreciated assets that can then be depreciated or amortized for tax purposes. In an asset purchase or in a transaction that is deemed to be an asset purchase for tax purposes (such as a Section 338(h)(10) transaction), the acquirer may amortize certain purchased intangibles under Section 197 provided that the acquirer holds those intangibles in connection with the conduct of a trade or business or in an activity for the production of income.[7] Section 197 was enacted in 1993 to implement a more uniform approach to the amortization of intangibles.

[7] All "Section" or "§" references are to sections of the Internal Revenue Code of 1986, as amended ("***Code***").

For intangibles that are subject to Section 197, the amortization of the tax basis is taken over a 15-year period on a straight line basis. This amortization period is established by statute and may result in cost recovery over a longer period than the expected or actual useful life of the intangible. Section 197 also imposes restrictions on taxpayer's ability to take a loss or worthlessness deduction for Section 197 intangibles that are disposed of if that intangible was acquired along with other intangibles in a transaction or series of related transactions until the taxpayer no longer retains any intangibles acquired in the relevant transaction(s).

For small high tech companies, attracting funding from investors as early as possible in the life-cycle of the company is of critical importance. This is especially true in the biotechnology industry where there is typically a significant time lag between commencement of research and FDA approval of a product (if such approval ever can be obtained). Earlier stage acquisitions of such companies by better-financed acquirers can mean the difference between making significant technological advances and an unsuccessful business. Properly targeted tax incentives can spur such earlier stage acquisitions.

Tax incentives can encourage investors contemplating acquisitions of the trade or business assets of high tech biotechnology businesses to purchase the business at an earlier stage in the company's developmental cycle. These companies typically have intangible assets that are amortizable under Section 197. Under the proposal, Section 197 would be amended to provide for faster cost recovery for intangible assets acquired by investors purchasing the trade or business of a qualified small high biotechnology company. The amendment is further proposed to provide that acquirers of such trade or business assets not be as restricted in their ability to take loss/worthlessness deductions for acquired Section 197 intangibles by amending the onerous limitation that currently exists.

Current Law

Section 197(a) permits taxpayers to amortize an "amortizable Section 197 intangible" ratably over a fifteen year period. An amortizable Section 197 intangible generally includes any "Section 197 intangible" that is acquired after August 10, 1993 and that is held in connection with the conduct of a trade or business or in an activity for the production of income. Section 197 intangibles include, without limitation, goodwill (Section 197(d)(1)(A)), going concern value (Section 197(d)(1)(B)), workforce in place (Section 197(d)(1)(C)(i)), business books and records, operating systems, or any other information base (Section 197(d)(1)(C)(ii)), and patents and know-how (Section 197(d)(1)(C)(iii)). Certain self-created intangibles, including goodwill and going concern value, are not treated as amortizable Section 197 intangibles unless they are created in a transaction or series of transactions involving the acquisition of assets constituting a trade or business.[8] The costs of these intangible may be deductible currently by the creator if

[8] A "trade or business" for purposes of Section 197 is defined by reference to Section 1060, which addresses the allocation of purchase price among the assets in an "applicable asset acquisition." An applicable asset acquisition is defined as the purchase of assets to which goodwill or going concern value can attach. For purposes of Section 197, a trade or business is similarly defined as assets to which goodwill or going concern value can attach. Treas. Reg. § 1.197-(2)(e)(1).

self-created, but must be amortized over 15 years under Section 197 if purchased as part of a trade or business.

There are exceptions to the applicability to Section 197, including for certain intangibles that were "acquired separately." Patents, copyrights, and any rights to receive tangible property or services under a contract are among the intangibles that are not Section 197 intangibles if they are not acquired in an acquisition of assets constituting a "trade or business" or a substantial portion thereof. Section 197(d)(4). Separately-acquired intangibles would be subject to depreciation/amortization under Code provisions other than Section 197.

Section 197(f) provides that a taxpayer cannot recognize a loss upon the disposition of a Section 197 intangible acquired in a transaction or series of related transactions in which the taxpayer acquired other Section 197 intangibles, if the other intangibles are retained by the taxpayer. In lieu of the loss, the taxpayer must increate the basis in the intangibles that it retains on a pro rata basis by the amount of the disallowed loss. Section 197(f)(1)(A); Treas. Reg. § 1.197-2(g). For purposes of these rules, the worthlessness of a Section 197 intangible is treated as a disposition. Section 197(f)(1)(A).

Proposed Changes:

Amortization
Amortizable Section 197 intangibles are amortized on a straight line basis over 15 years. This method of amortization contrasts with the faster depreciation that may apply to certain separately acquired intangibles and to many tangible assets, which often can be amortized/depreciated over a shorter period on an accelerated (*i.e.*, not straight line) basis. The proposal would shorten the recovery period for the costs of amortizable Section 197 intangibles acquired in connection with the acquisition of the trade or business assets (or a deemed purchase of the trade or business assets) of high tech and other research-intensive companies that are "qualified small high tech companies." The amortization period for such acquired intangibles would be reduced to 5-years and purchasers would be permitted to amortize their basis using the "double declining balance method" that is available for tangible assets. The double declining balance method of cost recovery is commonly used for depreciable property under the Code and would permit the faster recovery of the cost of such purchased intangibles.

Dispositions and Worthlessness
In some cases, amortizable Section 197 intangibles are sold or become worthless before the end of the 15-year amortization period. Section 197 prohibits a loss deduction or worthlessness deduction so long as other intangibles acquired in the same or related transactions are still held by the taxpayer. This rule is intended to prevent taxpayers from reducing the effective recovery period for intangibles from the 15-year amortization period by taking earlier write-offs. The proposal would permit acquirers of intangibles of qualified small biotechnology technology companies to deduct their adjusted basis in the disposed of/worthless intangibles at the later of three years or the time of the disposition/worthlessness rather than having to continue the amortization of those intangibles over the remaining amortization period of the retained intangibles. Due to the proposed shorter amortization period (5 years) and accelerated cost

recovery method, the restriction on loss/worthlessness dispositions is less relevant for policing the possibility of taxpayers significantly shortening their cost recovery periods from 15-years.

Trade or Business of a Qualified Small High Technology Business

The proposal would only apply to purchasers of trade or business assets from a qualified small biotechnology business. Thus, the separately acquired intangibles currently excluded from treatment as Section 197 intangibles would continue to be excepted from the application of Section 197. The proposal would apply to purchased goodwill, going concern value, customer and supplier-based intangibles, and would apply to patents, copyrights, and rights to goods or services under a contract that were acquired in an acquisition of a trade or business.

A qualified small biotechnology company would first have to meet a size restriction, and would be defined as: (1) any entity if the annual average number of employees employed by such person during either of the 2 preceding calendar years was 500 or fewer under Section 41(b)(3)(D)(iii) or (2) any entity that, if treated as a "C" corporation for federal tax purposes, meets the definition of a qualified small business under Section 1202(d), substituting a $150 million gross asset test (with special rules for taking into account intangible assets of the company). Controlled group rules would apply to ensure that the acquired companies for which this accelerated amortization and loss/worthlessness deductions would apply are appropriately limited to those that are in fact small businesses. Second, a qualified small high biotechnology company would have to meet a "biotechnology business" requirement. This would require the conduct of sufficient "qualified biotechnology research and development" to meet a minimum threshold amount.

The research and development prong would build off of the existing Section 41 research credit. Thus, the company's activities would need to meet the "qualified research" definition under Section 41(d)(1)(B). Specifically, the project would need to focus on research activities undertaken for the purpose of discovering information—

- which is technological in nature, and
- the application of which is intended to be useful in the development of a new or improved business component of the taxpayer.

This prong would also incorporate the standards used by the IRS in determining whether there is "qualified research" under Section 41(d) (*e.g.*, uncertainty, related to development/improvement, etc.), with appropriate modifications for purposes of this provision.

The biotechnology portion of the test would provide that the research and development conducted by the company must be in a recognized biotechnological field. This would be defined as a project designed to:

- Treat or prevent diseases or conditions by conducting pre-clinical activities, clinical trials, and clinical studies, or carrying out research protocols, for the purpose of securing FDA approval of a product under section 505(b) of the Federal Food, Drug, and Cosmetic Act or section 351(a) of the Public Health Service Act.

- Diagnose diseases or conditions or to determine molecular factors related to diseases or conditions by developing molecular diagnostics to guide therapeutic decisions.
- Develop a product, process, or technology to further the delivery or administration of therapeutics.
- Develop other projects in the biotechnology industry.

The minimum threshold amount of qualified biotechnology research and development would require that substantially all of the business activity of the company would consist of conducting research and development in the biotechnology field. "Substantially all" would be determined based on appropriate measures that are suitable for research and development small businesses, such as a specified ratio of research and development expenditures to product revenues.

ATTACHMENT II: INDUSTRIAL & ENVIRONMENTAL PROPOSALS

THE BIO-BASED ECONOMY JOBS AND DEVELOPMENT ACT

Background

The "Bio-based Economy" refers to economic activity and jobs generated by the use and conversion of agricultural feedstocks to higher value products, the use of microbes and industrial enzymes as transformation agents or for process changes, and the production of bio-based products and biofuels. This proposal seeks to elevate the concept and awareness of the bio-based economy and advance the policy priorities of the IES working groups, highlighting the outstanding job creation and rural/rust belt economic development potential of industrial biotechnology and biorefinery commercialization.

TABLE OF CONTENTS

TITLE I: AGRICULTURE

BIOMASS CROP ASSISTANCE PROGRAM – REAUTHORIZATION AND ENHANCEMENT

Background
An available, continuous and consistent supply of biomass for energy ("purpose grown energy crops" or "PGECs") is essential to the continued development of the domestic biofuels and bio-products industries. However, the development of such a supply is challenging for many reasons, including hesitation by farmers and landowners to produce PGECs on high-yielding farmland where traditional crop rotations exist, as well as concern about lack of a mature market. Congress has recognized the need for PGECs and has enacted several pieces of legislation in recent years to address these challenges.

One of the most important and effective programs to this end is the Biomass Crop Assistance Program (BCAP), established under the Food, Conservation, and Energy Act of 2008 (P.L. 110-246, 2008 Farm Bill). BCAP is set to expire on December 31, 2012. Assuming spending authority for BCAP will be reauthorized in a 2012 Farm Bill, USDA predicts that over the next ten years BCAP will create 70,000 jobs and will generate $80 billion in economic activity.

BCAP is designed to incentivize and facilitate development of a sustainable supply of biomass from energy by (1) supporting the establishment and production of eligible crops for conversion to bioenergy in selected areas, and (2) assisting agricultural and forest land owners and operators with collection, harvest, storage, and transportation of eligible material for use in a biomass conversion facility.

Although BCAP was established in the 2008 Farm Bill, USDA did not publish its final rule implementing the program until October 22, 2010. The rule is designed to promote production of PGECs on approximately 17 million acres of traditional farmland and 34 million acres of pastureland. Since the rule was published, the USDA has been working diligently to disseminate BCAP funds to eligible parties, including farmers. However, BCAP must continue to be fully funded and reauthorized so its full potential to spur production of the requisite supply of PGECs for the growth of the biofuels and bio-products industries may be realized.

Proposal
This section reauthorizes the BCAP program through December, 2017, with funding through the Commodity Credit Corporation at such sums as necessary. In addition, this section provides for several clarifying amendments to (1) ensure funds are directed primarily to production of next generation crops for biofuels and bioenergy; (2) establish a dedicated funding mechanism for awarded contracts; (3) provide for eligibility of non-food Title I crops; and (4) clarify eligibility of certain other PGECs.

FEDERAL CROP INSURANCE FOR PURPOSE GROWN ENERGY CROPS

Background

Recent laws and Congressional proposals have sought to promote the development and commercialization of domestic sources of energy, including biofuels. One way to accomplish this goal is to increase domestic production and growth of dedicated crops to be used solely for energy (purpose grown energy crops, or PGECs). In order to increase the yields of such crops, U.S. farmers must decide to grow them. One deciding factor is the availability of crop insurance that will cover these new PGECs because, generally, banks and investors require crop insurance as collateral to approve operating loans for farmers that would cover the cost of the seed.

The 2008 Farm Bill directed the U.S. Department of Agriculture's (USDA) Risk Management Agency (RMA) to study the feasibility of developing crop insurance programs for biofuels feedstocks. While RMA is currently studying the feasibility of providing insurance for six specific PGECs, no formal program has been created to date. One must be established in the near term to keep up with the momentum and demand for the development of greater domestic sources of energy.

Proposal

Direct the USDA Risk Management Agency to (1) finalize research on the feasibility of providing crop insurance to producers of corn stover, straw and woody biomass, as well as energy cane, switchgrass and camelina, and (2) utilize that research to work with stakeholders, including industry and policymakers, to establish by January 1, 2013, a formal crop insurance program that will cover those six PGECs. Direct the RMA to also address a broader range of PGECs to be covered by crop insurance.

Authorize and provide such sums as necessary from the Commodity Credit Corporation to carry out the crop insurance objectives described above. In addition, authorize and provide $25 million annually from the CCC for the RMA to carry out a PGEC insurance education/outreach campaign for growers.

FEEDSTOCK SUSTAINABILITY ENHANCEMENT GRANTS

Background

The continued development of domestic sources of energy, including for biofuels and renewable chemicals, depends upon the sustainable availability of consistent, high yield, good quality feedstocks. At the core of producing sustainable feedstocks is carefully selecting crops that can meet this nation's bioenergy needs, while remaining both good for the environment and for the farmers that produce them.

The Department of Energy's Offices of Biomass and Science, along with the U.S. Department of Agriculture (USDA) have done important research to help identify sustainable dedicated energy crops, and to help enhance the sustainability of currently available feedstocks. For example, there is increasing evidence that winter cover crops could provide a significant supply of

sustainable feedstocks for energy, while simultaneously offering great environmental benefits and financial potential for farmers.

Proposal
Establish a grant program through the U.S. Departments of Agriculture and Energy to fund demonstration projects, including cover crops, that will utilize and show various practices that could enhance biofuels and bioenergy feedstock sustainability. Authorized at $50 million annually through 2017.

FARM BILL ENERGY TITLE AMENDMENTS FOR RENEWABLE CHEMICALS

Background:
Title IX of the 2008 Farm Bill contains several programs to accelerate commercialization of renewable energy technologies to reduce dependence on imported oil, revitalize rural economies, and enhance energy security. But many of the programs are not available to renewable chemicals and bio-based products, which offer the same benefits to rural America. In developing commercial scale biorefineries, renewable chemicals and biofuels should receive incentive parity. Farm Bill Energy Title programs should be opened to renewable chemicals and bio-based product projects.

Proposal:
BIO proposes modifying the 2008 Farm Bill by: a) adding a definition for "renewable chemicals" under Section 9001, in order to codify precisely what is meant by the term, so that law makers and industry participants are able to reference a legal authority and establish a standard for renewable chemicals in the biotechnology industry; b) amending section 9002 by implementing market awareness and acceptance of the renewable chemicals and bio-based products in the procurement program of the BioPreferred™ Program and increasing the mandatory funding to $10 million, annually through 2017, and additional discretionary funding to $10 million, annually through 2017; c) amending section 9003, USDA's Biorefinery Assistance Program by adding renewable chemicals at each reference to advanced biofuels, and increasing the maximum amount of loan guarantee to $500MM through 2017; d) amending section 9007, Rural Energy for America Program (REAP) by adding renewable energy technologies that also include energy efficient renewable chemicals and advanced biofuels manufacturing processes; e) amending section 9008 by adding the definition of renewable chemicals at each reference of bio-based products.

TITLE II: TAX

Tax Credit for Production of Qualifying Renewable Chemicals

Background:
Renewable chemicals and bio-based plastics represent an important technology platform for reducing reliance on petroleum, creating green U.S. jobs, increasing energy security, and reducing greenhouse gas emissions. By providing a renewable chemicals tax credit, Congress can create jobs and other economic activity, and can help secure America's leadership in the important arena of green chemistry. Most chemicals and plastics used today are made from petroleum. Advances in industrial biotechnology have led to renewable chemicals and bioplastics from renewable feedstocks that are providing innovative new products. Currently, bioplastics are used in everything from cups to carpets to cars, green airplane deicing compounds and cosmetics. Most of these products are competing in markets presently dominated by petroleum based products, and renewable chemicals still make up only a small percentage of total chemicals and plastics sales. The US has the potential to become the world leader in renewable chemicals, as we are currently home of the most advanced in renewable chemicals technology and intellectual property, and have access to a wide range of renewable feedstocks that can be sustainably produced. Renewable chemicals represent a historic opportunity to revitalize the U.S. chemicals and plastics industry, which has seen hundreds of thousands of jobs move overseas in the past decade. While U.S. policy has appropriately encouraged and supported the development of the biofuels sector to the benefit of rural economies, the environment, and national security, federal tax policy has largely failed to recognize and foster the substantial benefits provided by non-fuel renewable chemicals.

Proposal:
BIO proposes a federal income tax credit for renewable chemicals: a) that are domestically produced from renewable biomass; and like current law renewable electricity production credits, the credits would be general business credits available for a limited period per facility; b) similar to the operation of IRC section 48C, the Treasury Department and USDA would review taxpayers' applications in a competitive process to ensure conformance with legislative intent; c) producers found eligible to participate in the program will receive an allocation from a pool of credits based upon qualified production performed after date of enactment; and no credits will be allocated for production before date of enactment; d) which are composed of no less than 25% bio-based content will be eligible for production credits; e) per calendar year, each taxpayer would be entitled to claim as much as $25MM in renewable chemicals production tax credit associated with production of eligible renewable chemicals.

ADVANCED BIOFUELS TAX REFORM

Background:
Current tax law on advanced biofuels does not provide an ordered pathway toward U.S. energy security. Congress must consider amendments to the current law tax incentives that focus on:

- Displacing foreign oil and gas
- Bringing commercial volumes of affordable advanced biofuels to market in the near term
- Lowering our greenhouse gas footprint
- Increasing our environmental sustainability of feedstocks
- Technology-Neutral incentive mechanisms
- Calculating incentive value on a performance-basis

Proposal:
The Cellulosic Biofuel Production Tax Credit expires on 31 December 2012, before commercial facilities can be placed in service. Congress should extend the credit through 2016. Additionally, the credit should be renamed the "Next Generation Biofuel" credit, and algal biofuels should be made eligible for the PTC. A special rule should allow bio-crude producers to obtain the PTC.

The Code should be amended to allow advanced biofuel facility developers the option of electing to receive an investment tax credit. Eligibility would be limited to advanced biofuels that meet federal GHG reduction standards of Section 211(o) of the Clean Air Act, and which are not currently produced on commercial scale.

A special rule in the Investment Tax Credit should clarify the eligibility of projects that convert traditional biofuel plants to advanced biofuels. The objective of the rule would be to encourage the rapid deployment of the first billion gallons of capacity of advanced biofuels.

Just like wind, solar and geothermal facilities, advanced biofuel facilities can be expected to encounter severe difficulty in monetizing the new federal ITC. For this reason, advanced biofuels ITCs should be made eligible for the federal Section 1603 Grants in Lieu of Tax Credits program.

Current law allows for 50% bonus depreciation for cellulosic biofuel production property. Congress should modify Section 168(l) to extend the program through 2016 and to harmonize the definition of eligible property to match that encompassed by "Next Generation Biofuel Property."

TITLE III: DEFENSE

STRATEGIC BIOREFINERY INITIATIVE AND OFFTAKE AUTHORITY

Background

The Department of Defense (DOD) is a significant consumer of fuel and other petroleum-based products, representing close to 2 percent of annual U.S. petroleum use. The military is therefore at the mercy of the market – both in terms of stability of supplies and fluctuations in price. Substantial energy security benefits would accrue to the Department of Defense from development of domestic sources of renewable biofuels and bio-based products. The DOD and individual branches of the U.S. military have recognized the importance of diversifying their fuel supply. The DOD's objective is to acquire 50 percent of its domestic jet fuel from alternative fuel blends by 2016. The U.S. Navy has set a target to fuel half of all of its energy needs with non-fossil fuel sources by 2020. In March, President Obama directed the Navy, DOE and USDA to work with the private sector to accelerate deployment of advanced biofuels for military use.

Advanced biofuels for military use are rapidly approaching commercialization, with demonstration projects online. For example, Solazyme delivered to the Navy the largest amount of advanced biofuel (20,000 gallons of jet and diesel) ever produced, and has a contract to deliver over seven times more fuel in 2011 – 150,000 gallons.

The greatest barrier to large-scale commercial production of military biofuels remains access to capital for construction of first-of-a-kind next generation biorefineries. As a major potential customer and as a potential source of funding for biorefinery construction, the DOD is uniquely positioned to help accelerate deployment of advanced biofuels. The DOD should fund construction of the first five commercial military advanced biofuel biorefineries to rapidly accelerate deployment. Congress should also provide DOD with long-term offtake authority for advanced biofuels to assist subsequent project developers in attracting private capital for biorefinery construction.

Proposal

A strategic biorefinery initiative is needed to accelerate deployment of advanced biofuels for military use. This section establishes and provides necessary funding for a DOD Strategic Biorefinery Deployment Program to finance construction of the first 5 commercial military advanced biofuel biorefineries. It directs DOD to identify existing funding authority for such projects, and to conduct by January 1, 2012, a biorefinery "fly-off" to identify and fund construction of the most promising projects. Evaluation criteria should include (1) commercial viability; (2) strategic / tactical value; and (3) compliance with EISA Sec. 526 greenhouse gas requirements.

In addition, this section provides DOD with the authority to enter into long-term (up to 15 years) offtake agreements for procurement of advanced biofuels for military use. Adopt language from H.R. 1847 of the current Congress.

TITLE IV: ENERGY

REPURPOSE AND RETROFIT GRANT PROGRAM

Background

Availability of supportive infrastructure is one of the greatest practical and economic challenges that will determine the growth and success of the advanced biofuels industry. As this industry matures, so does the pressing need for facilities and equipment to support its development from inception to market. At the same time, this country and the momentum of the advanced biofuels industry cannot afford the time and cost of building all new infrastucture. The great news is that many companies have and are developing advanced biofuels and renewable chemical technologies that can be used with existing idled or underutilized U.S. manufacturing facilities.

It is widely recognized that repurposing or retrofitting those facilities to integrate next generation processes capable of producing advanced biofuels and renewable chemicals and bio-products is one of the most time and cost effective ways to build out the advanced biofuels and renewable chemicals sector. It is also the fastest way to advanced biofuels commercialization that will lead to fulfillment of alternative fuel usage requirements under the federal Renewable Fuel Standard (RFS).

Depending on the advanced process and technology involved, industry efforts are underway to repurpose or retrofit several types of idled or underutilized manufacturing facilities, including first generation ethanol facilities, biodiesel refineries and pulp and paper mills. For example, Gevo, Inc., is retrofitting existing ethanol plants to produce isobutanol and hydrocarbons. Cetene Energy is integrating hydroprocessing capacity into an existing biodiesel refinery. And, Cobalt Technologies is working on retrofitting outdated pulp and paper mills to use existing feedstocks from those mills to make advanced biofuels.

Repurposing or retrofitting existing manufacturing facilities is not only the most efficient way to facilitate the development and commercialization of advanced biofuels and renewable chemicals to help increase U.S. energy independence and security, but it offers a wide variety of additional benefits to the nation. It reenergizes local economies by repurposing existing industrial assets, and retaining and creating jobs.

Proposal

Establish a federal matching grant program through the U.S. Department of Energy to fund projects to repurpose or retrofit existing idle or underutilized manufacturing facilities for the production of advanced biofuels and/or renewable chemicals. Grants would be eligible for up to 30 percent of eligible costs. Authorized at $100 million annually through 2017.

Private companies will be able to leverage this support to attract greater private investment in retrofit projects that will enable faster commercialization of advanced biofuels and renewable chemicals.

SYNTHETIC BIOLOGY FOR ENHANCED SUSTAINABILITY OF BIOFUELS AND RENEWABLE CHEMICALS

Background:
The advancing field of synthetic biology has the potential to transform the U.S. economy by fundamentally changing the way we make and use chemicals and materials. By rapidly testing prototype biological systems with a speed and complexity not previously feasible or cost effective, synthetic biology can be applied to help resolve important challenges in synthesizing new products, whole cell systems, and other biologic processes in ways that can enhance both the economic and environmental sustainability of fuels and chemicals manufacturing. In the chemicals sector, the production of chemicals using engineered microorganisms and enzymes could generate global revenues of $1 trillion and create 1.2 million direct jobs. Additional revenue and job creation will occur as synthetic biology delivers advanced biofuels and pharmaceutical intermediates for the healthcare industry.

As with most product development, innovation and competitiveness can often be tied to the ability to rapidly and predictably obtain optimum performance outcomes. Synthetic biology offers this promise to academic research groups, government technology institutes, and to public and private corporations seeking to develop biological solutions to today's challenging needs in fields such as advanced biofuels and renewable chemicals.

Proposal:
BIO proposes the establishment of a DOE Synthetic Biology Research and Development (R&D) Grants Program to fund research and development in industrial biotechnology for the enhanced sustainability of biofuels and renewable chemicals produced through synthetic biology technology. This program would work towards breakthroughs, yield new knowledge, and lead to the design of biological catalysts and processes that would enable the cost-effective sustainable production of: (a) advanced biofuels and renewable chemicals from renewable biomass (as defined in 2008 farm bill); and (b) other technologies that reduce or minimize greenhouse gas emissions, including biological processes for removing carbon dioxide from the atmosphere. BIO proposes $20M be authorized annually for this program through 2017.

INDUSTRIAL BIOPROCESS R&D PROGRAM

Background:
The use of industrial biotechnology for the production of renewable chemicals and bio-based products is enabling dramatic improvements in industrial energy efficiency as well as a host of renewable alternatives to traditional petrochemical-based products. These technologies have the potential to create high-value domestic green jobs, reduce the United States' trade balance, reduce greenhouse gas (GHG) emissions, and enhance energy security by reducing dependence on imported oil. To date, however, federal investment in research and development for industrial biotechnology for non-fuel applications has been minimal. The U.S has the potential to become the world leader in the renewable chemicals and bio-based products markets, as we are currently home to the most advanced renewable chemicals technology and intellectual property and have

access to a wide range of renewable feedstocks that can be sustainably produced. Renewable chemicals based products represent a historic opportunity to revitalize the U.S. chemicals and plastics industry, which has seen hundreds of thousands of jobs move overseas in the past decade. The renewable chemicals industry has created or saved 40,000 jobs thus far, and achieving the industry's full potential could create tens of thousands of additional high-paying green jobs in the US over the next few years.

Proposal:
BIO proposes the establishment of an Industrial Bioprocess Research & Development (R&D) program through the Department of Energy (DOE), Office of Energy Efficiency and Renewable Energy (EERE), Industrial Technologies Program (ITP), to fund projects in industrial biotechnology for renewable chemicals, bio-based products, and renewable specialty chemicals.

Given industrial biotechnology's unique ability to improve both the efficiency and sustainability of chemical manufacturing, the EERE Office of Industrial Technologies Program (ITP) would be a natural home for such funding. This program would provide grants for the demonstration of advancements in energy efficiency and the reduction of greenhouse gases (GHG) through: a) process improvements showing increases in energy efficiency of existing process systems and/or reduction of lifecycle GHG emissions from the development of new biocatalysts (enzymes or microorganisms); b) basic research leading to process development that involves either biological or chemical conversion of sustainable feedstocks into renewable chemicals and show an increase in energy efficiency and/or reduction of lifecycle GHG emissions; c) research and development of new processes to utilize sustainable feedstocks (or pure sugar as feed) for manufacturing renewable chemicals that show an increase in energy efficiency against an existing industrial petrochemical manufacturing standard; d) basic research leading to development of processes to utilize sustainable feedstocks (or pure sugar as feed) for manufacturing renewable chemicals that show an increase in energy efficiency against an existing industrial petrochemical manufacturing standard. BIO proposes authorizing $150M annually through 2017.

Title V: Environment

EPA R&D Program for Renewable Chemicals

Background:
Though most chemicals and plastics used today are petroleum-based, rapid advancements in industrial biotechnology are providing petrochemical alternatives by utilizing renewable feedstocks. These renewable chemicals and bioplastics are used in a growing number of everyday products such as cups and carpets, deicers, detergents, personal care products, food and flavoring ingredients, pharmaceutical intermediates, composites, adhesives, sealants, coatings, additives, lubricants, and insulating materials.

Renewable chemicals can be engineered to provide innovative solutions that save energy, are environmentally preferred, and are a direct substitute or "drop-in" replacement for petrochemicals. Domestically produced high-volume drop-in replacement renewable chemicals would show how industrial biotechnology is reducing consumption of petroleum resources, reducing waste, and improving sustainability. Presently, there are no strong standardized metrics. If the EPA had energy data or generated such data for benchmarking petrochemical processes, life cycle analysis (LCAs) models could be produced. These LCAs would allow renewable chemical companies to demonstrate substantial cost, environmental, and efficiency benefits which could be added to partnering and investment brochures that would assist in further encouraging the development of sustainable products in the U.S.

Proposal:
BIO seeks to establish a new Research and Development (R&D) program funded by the Environmental Protection Agency (EPA) that would provide grants to conduct environmental assessments for renewable chemicals and industrial products produced with industrial biotechnology processes. This program would (1) conduct assessments to provide quantitative data to demonstrate chemical safety and pollution prevention in industrial biotechnology processes; and (2) be followed up with educational and awareness programs for U.S. businesses for the purpose of providing education and data on the environmental and economic benefit of using green chemistry and biological processes in manufacturing. BIO is requesting $30M to be authorized annually through 2017.

ATTACHMENT III: FDA REGULATORY ENVIRONMENT PROPOSALS

CREATING A 21ST CENTURY FDA

ELEVATING FDA AND EMPOWERING OPERATIONAL EXCELLENCE

UPDATE THE FDA MISSION STATEMENT

Executive Summary

The Food and Drug Administration (FDA) needs a clear mandate to encourage the development of innovative products. In addition, FDA must have the capacity and commitment to incorporate the latest scientific advances into its decision making so that regulatory processes can keep pace with the tremendous potential of companies' leading edge science. Congress can help by updating FDA's statutory mission to underscore the need for FDA to advance medical innovation by incorporating modern scientific tools, standards, and approaches, so that innovative products can be made available to those who need them.

Background

FDA's mission, as set forth in section 1003 of the Federal Food, Drug, and Cosmetic Act (FFDCA), is to promote and protect the public health. FDA is charged with promoting the public health by "promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner." FDA also is charged with protecting the public health by ensuring the safety, and where appropriate, effectiveness of FDA-regulated products and protecting the public from electronic product radiation. However, the FDA mission statement fails to mention the agency's critical role in incorporating modern scientific advances into review practices to ensure that innovative treatments and therapies are made available to the patients that need them.

FDA should continually strive to remain on the cutting edge of science. Developments in modern science, such as personalized medicine, have the potential to yield innovative, safe, and effective new therapies by better targeting medicines to patients that need them. FDA's mission should reflect the importance of a modern agency that is equipped to respond to advances in science that can benefit the public health. Amending the FFDCA to update FDA's mission will keep FDA focused on, and accountable to, this important principle.

Proposal

To subparagraph (b) of section 1003 of the FFDCA:

(b) MISSION. — The Administration shall —

(1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;

(2) with respect to such products, protect the public health by ensuring that —

(A) foods are safe, wholesome, sanitary, and properly labeled;
(B) human and veterinary drugs are safe and effective;
(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;
(D) cosmetics are safe and properly labeled; and
(E) public health and safety are protected from electronic product radiation;

(3) advance medical innovation, and strive to make novel products available to those who need them, by incorporating modern scientific tools, standards, and approaches to ensure the timely and effective review, and approval as appropriate, of innovative treatments, therapies, devices and other regulated products;

~~(3)~~ **(4)** participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and

~~(4)~~ **(5)** as determined to be appropriate by the Secretary, carry out paragraphs (1) through ~~(3)~~ **(4)** in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

ESTABLISH A FIXED TERM OF OFFICE FOR THE COMMISSIONER OF FOOD AND DRUGS

Executive Summary

The Commissioner of Food and Drugs is charged with leading a science-based, regulatory agency to advance the public health. As required by statute, the President appoints the Commissioner with the advice and consent of the Senate. However, a presumption of replacement with each new President has politicized the appointment and confirmation process. The Federal Food, Drug, and Cosmetic Act (FFDCA) should be amended to provide that the President appoint the Commissioner to a six- year term of office. Once confirmed, the Commissioner would be removable by the President only for pre-specified reasons — neglect of

duty, malfeasance in office, or an inability to execute the mission of the Food and Drug Administration (FDA). Encouraging consistent and stable leadership at FDA, with protection from political influence that typically occurs during a presidential administration transition, better equips the agency to fulfill its mission to protect and promote the public health.

Background

FDA is a large, complex regulatory agency and requires stable leadership to effectively promote and protect public health. The Commissioner plays a critical role in setting direction for the agency, by encouraging empirically-based, scientifically sound decisions that allow FDA to achieve its public health mission.

Over the last 35 years, however, FDA has had ten Commissioners (including current Commissioner Hamburg) and nine acting Commissioners. The short tenure of the previous Commissioners and acting Commissioners has hampered the ability of the agency to advance policy initiatives or implement any sustained or long-lasting change. Further, significant turnover has subjected the agency to accusations of undue political influence and provided the opportunity for the politicization of approval decisions.

The FFDCA requires that the President appoint the Commissioner with the advice and consent of the Senate. However, it fails to provide a term of office for the Commissioner position. Appointing the Commissioner for a fixed term that is out of sync with, and longer than, the Presidential term should lessen turnover in this position, and it could lead to more stability in other leadership positions at the agency that are typically filled by each incoming President. Although FDA would remain part of the Executive Branch and within the Department of Health and Human Services, a six-year term of office for the agency's head — while the Administration is subject to a four-year term — would inherently insulate the office from the political process itself. It should also help to ensure continuity in agency initiatives and stability of agency priorities even when the Administration changes. Finally, the fact that a Commissioner under consideration would likely serve well into the term of the next President could help to ensure that the selection and confirmation process prioritizes scientific and managerial credentials over political ideology.

The President appoints individuals to other department and agency positions for a fixed term. For example, the Director of the Federal Bureau of Investigation is appointed for a ten-year term, the Commissioner of the Social Security Administration for a six year term, the Director of the National Science Foundation for a six year term, and the Commissioners of the Federal Communications Commission for five year terms.

Proposal

To subsection (1) of subparagraph (d) of section 1003 of the FFDCA:

(d) COMMISSIONER**.** —

(1) APPOINTMENT**.** — There shall be in the Administration a Commissioner of Food and Drugs (hereinafter in this section

referred to as the "Commissioner") who shall be appointed by the President by and with the advice and consent of the Senate. **The Commissioner shall be appointed for one term of six years, subject to removal by the President only for neglect of duty, malfeasance in office, or an inability to execute the mission of the agency**.

GRANT FDA STATUS AS AN INDEPENDENT AGENCY

Executive Summary

The FDA regulates nearly a quarter of the consumer goods supplied to the American public. As such, the agency should have the same authorities to make budget, management and operational decisions as afforded other independent agencies such as the Environmental Protection Agency. This would empower the agency to work more effectively with the President and Congress to carry out its mission to promote and protect the public health. Creating an independent agency would also enhance the agency's ability to obtain quality and consistent leadership.

Background

In its hundred year history, the FDA has been housed within a federal department, starting with the Department of Agriculture and then the Department of Health and Human Services (HHS) and its precursors. As a result, the agency has always been subject to the management, budgetary restrictions, and oversight of its parent department. In the meantime, several other high-impact regulatory agencies with powers to supervise certain sectors of the economy have been granted status as an independent agency, including the Environmental Protection Agency (EPA), the Social Security Administration (SSA), the Consumer Product Safety Commission (CPSC), the Federal Communications Commission (FCC), the Federal Trade Commission (FTC), and the Commodity Futures Trading Commission (CFTC). In 1987, Senator Al Gore (D-TN) pursued legislation that would have made FDA a virtually independent Agency within HHS, but that proposal was not approved. In 1990, the Edwards Commission also proposed either elevating FDA within HHS or making it an independent agency separate from the department or the Public Health Service.

If the FDA were to become an independent agency, it would increase the agency's position and profile within the Executive Branch and correspondingly increase the profile of the Commissioner of Food and Drugs, which may also enhance FDA's ability to supervise its sector. In addition, the FDA would have more freedom in its budget request since it would no longer be required to go through the department budget process, which often requires agencies to curtail their overall budget requests. It is critical that if FDA were to become an independent agency, it continue to coordinate appropriately with other HHS operating divisions such as the National Institutes of Health, the Centers for Disease Control, the Centers for Medicare and Medicaid Services, and the Agency for Healthcare Research and Quality.

Establishing a new independent federal agency would require an act of Congress.

Proposal

Establish FDA as a free-standing, independent agency outside of the departments of the executive branch, as defined under §104, Title 5 of the United States Code.

ESTABLISH AN EXTERNAL MANAGEMENT REVIEW BOARD FOR FDA

Executive Summary

The Food and Drug Administration (FDA) is a large, complex organization responsible for regulating nearly a quarter of the consumer goods supplied to the American public. To fulfill its responsibilities effectively, FDA must be well organized and well managed. It is critical that the agency's organization and management capabilities are periodically analyzed and that the Commissioner of Food and Drugs be provided with fresh, visionary, and independent thinking on how to improve the ability of the agency and its centers to promote and protect the public health, as well as the support necessary to implement recommendations. An external advisory board composed of individuals with experience in organizational management could help the agency address operational challenges. The Federal Food, Drug, and Cosmetic Act (FFDCA) should be amended to establish a Management Review Board (MRB) to conduct periodic reviews of FDA's management and organizational structure and provide recommendations to the Commissioner about ways to improve FDA operations.

Background

The substantial size of FDA presents a challenge to agency leadership. FDA consists of six product centers, one research center, and two offices. It employs over 11,500 full time equivalent (FTE) staff across the world. FDA has employees posted in China (Beijing, Shanghai, and Guangzhou), India (New Delhi and Mumbai), Costa Rica (San Jose), Chile (Santiago), Mexico (Mexico City), and Belgium (Brussels). The agency is responsible for regulating more than $2 trillion in food, drugs, medical devices, cosmetics, dietary supplements, and other consumer goods—nearly a quarter of the U.S. consumer goods supply.

Since the passage of the 1906 Food, Drug, and Cosmetic Act, new statutory requirements have significantly expanded FDA responsibilities. Beginning in the 1950s and through the 1970s, Congress required FDA to review and approve, prior to marketing, the safety and effectiveness of human new drugs, animal new drugs, human biological products, medical devices for human use, and infant formula products as well as review and approve the safety of human food additives, color additives, and animal feed additives.

In the 1980s through the 1990s, Congress required FDA to establish a pathway for approval of generic drugs, implement a framework to identify and designate products as promising treatments for rare and neglected diseases (orphan drug program), approve disease prevention and nutrient descriptor claims for food products, and develop a program providing expanded access to investigational drugs. Congress also required FDA to review new dietary supplement ingredients prior to marketing and authorized the agency to establish good manufacturing practice regulations for dietary supplements.

More recently, the Food and Drug Administration Amendments Act of 2007 imposed substantial new requirements on FDA in a range of areas, including medical product safety, advisory committee membership and recruitment, and clinical trial registries. In June 2009, FDA was granted authority to regulate tobacco products. The Patient Protection and Affordable Care Act enacted in March of 2010 requires FDA, among other things, to establish a pathway for approval of biosimilar biological products. Most recently, in January 2011, the FDA Food Safety and Modernization Act (FSMA) provided FDA with tools to improve the agency's ability to prevent contamination in the food supply.

The globalization of the medical product and food industries also challenges FDA. The agency estimates that 80% of the active pharmaceutical ingredients (API) in drugs and approximately 40% of the finished products are imported. FDA estimates that the agency regulates $49 billion worth of imported foods. High profile recalls involving substances that originated overseas, such as the contamination of the API used in heparin, a blood thinning drug, and the contamination of pet food with melamine, underscore the challenges FDA faces in this area.

The size and complexity of the FDA, increasing statutory responsibilities, and globalization of FDA-regulated industries have placed significant demands on FDA and may have hampered its ability to develop forward-thinking strategies. For example, FDA does not have a comprehensive information technology (IT) infrastructure that allows it to track information. To the extent IT systems exist, they often do not readily interact with each other. Data must be analyzed manually at times. Without an efficient means to accurately collect and analyze information, FDA cannot make data-driven decisions, or build upon past experience to systematically plan future activities to best advance the public health. Limited resources exacerbate these management and organizational shortcomings, and hamper FDA's ability to achieve its public health mission.

The establishment of an external management review board could help identify deficiencies in FDA's management and organizational structures that threaten the agency's ability to meet its numerous regulatory responsibilities. The creation of review board to advise an agency on management and organizational issues is not unprecedented. For example, the National Institutes of Health (NIH) Reform Act of 2006 established a Scientific Management Review Board (SMRB) to advise the NIH Director and other appropriate officials on the use of certain statutory authorities to reorganize NIH to carry out its activities more efficiently. The NIH SMRB helps to ensure that NIH's structure is optimal for supporting the advancement of science.

Proposal

To help FDA strategically manage its operations, FFDCA should be amended to create an external Management Review Board (MRB) to undertake a formal regulatory process review and improvement initiative, and make recommendations to the Commissioner on needed improvements to FDA's management structure and organization. The MRB would be governed by the Federal Advisory Committee Act (FACA), which sets forth the rules under which all federal advisory committees operate. Meetings of the MRB would be noticed in advance, and would generally be open to the public, except in the limited situations where proprietary information, classified information, or personal privacy interests were implicated. Further, members of the public could provide comments to the MRB, and records from the MRB

meetings would be available to the public for inspection. The success of the MRB will be highly dependent on the personal and committed involvement of FDA senior leadership, including the Commissioner of Food and Drugs, in recruiting highly qualified, visionary and independent thinkers to serve on the MRB; alternatively, an outside body might be charged with recruiting members and/or convening the board.

To Chapter 7, Subchapter A of the FFDCA:
Sec. 714. Management Review Board.
(a) IN GENERAL. — Not later than 60 days after the passage of this act, the Secretary shall establish an advisory committee with the Food and Drug Administration to be known as the Management Review Board (referred to in this section as the "Board").

(b) DUTIES. —
(1) REPORTS ON MANAGEMENT ISSUES.— The Board shall provide advice to the Commissioner regarding the management and organization of the Food and Drug Administration. Not less frequently than once each 6 years, the Board shall —

(A) determine whether and to what extent changes should be made to the management and organization of FDA; and

(B) issue a report providing the recommendations of the Board regarding the changes to management and organization and the reasons underlying the recommendations.

(2) TOPICS.—
(A) The Commissioner may submit requests about management or organizational issues to the Board for assessment.

(B) The Board shall seek input from the public on management and organizational issues it would be helpful to assess.

(c) COMPOSITION OF BOARD.—
(1) The Board shall consist of the Commissioner, who shall be a permanent nonvoting member on an ex officio basis, and an odd number of additional members, not to exceed 21, all of whom shall be voting members. The voting members of the Board shall be the following—

(A) Not fewer than 9 officials who are directors of the product centers, directors of FDA divisions, or members of the FDA Science Board. The Secretary shall designate such officials for membership.

(B) Members appointed by the Secretary from among individuals who are not officers or employees of the United States for a three-year term, which could be renewed once. Such members shall include—

(i) individuals representing the interests of public or private institutions of higher education;
(ii) individuals representing the interests of the industry; and
(iii) individuals with broad expertise regarding how FDA functions and experience successfully managing large scientific organizations (exclusive of private entities to which clause (i) applies).

(d) CHAIR.— The Chair of the Board shall be selected by the Secretary from among the members of the Board appointed under subsection (c)(1). The term of office of the Chair shall be 2 years.

(e) MEETINGS.—
(1) In general. — The Board shall meet at the call of the Chair or upon the request of the Commissioner, but not fewer than 5 times with respect to issuing any particular report under subsection (b)(1). The location of the meetings of the Board is subject to the approval of the Commissioner.

(f) REPORTS.—
(1) Each report under subsection (b)(1) shall be submitted to—

(A) the Committee on Energy and Commerce and the Committee on Appropriations of the House of Representatives;

(B) the Committee on Health, Education, Labor, and Pensions and the Committee on Appropriations of the Senate; and the Secretary.

(2) AVAILABILITY TO THE PUBLIC.— The Commissioner shall post each report under subsection (b)(1) on the Internet site of the Food and Drug Administration for public comment.

(3) IMPLEMENTATION. Within 100 days, FDA shall begin to implement the recommendations set forth in each report under subsection (b)(1), and the recommendations shall be fully implemented within 3 years, except when the Commissioner objects to any recommendation or if Congress passes a joint resolution overriding the recommendation.

ADVANCING REGULATORY SCIENCE & INNOVATION

SUPPORT REGULATORY SCIENCE PUBLIC-PRIVATE PARTNERSHIPS

Executive Summary
Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress established the Reagan-Udall Foundation for the Food and Drug Administration, an independent nonprofit organization intended to support public-private partnerships for the purpose of

advancing the mission of the Food and Drug Administration (FDA) to "modernize medical [and other] product development, accelerate innovation, and enhance product safety."[9] The Foundation could, for example, form collaborations to advance the use of biomarkers, surrogate markers, and new trial designs to improve and speed clinical development. However, Appropriations bills have subsequently restricted FDA's ability to transfer federal funding to the Foundation. These funding restrictions should be lifted so that the Reagan-Udall Foundation can fulfill its promise.

Background

The FDAAA legislative history indicates that Congress envisioned the Foundation as helping to foster the development of new research tools to aid in the evaluation of the safety and effectiveness of drugs, biologics, and medical devices.[10] Congress viewed the Foundation's use of public-private partnerships and other research collaborations as "a way to develop [new research] tools – not so they can help just one researcher or one company, but so they can help the entire research enterprise."[11] FDAAA provides detailed information on the composition and activities of the Foundation, including its duties, Board membership, governance, funding, and requirements for assuring accountability.[12]

The duties of the Foundation include the identification of unmet needs for the development, manufacture, and evaluation of drugs, biologics, and devices (including diagnostics), and establishing goals and priorities to meet these needs. They also include providing "objective clinical and scientific information to the [FDA] and, upon request, to other Federal agencies to assist in agency determinations of how to ensure that regulatory policy accommodates scientific advances and meets" the Agency's public health mission.

Unfortunately, the Foundation has yet to receive any congressional appropriations. This is in large part due to concerns regarding accountability, including allegations that industry would have too much influence over the Foundation's activities. However, FDAAA required the Foundation to establish policies on conflicts of interest (and many other) standards. The Foundation's Board of Directors[13] has adopted bylaws[14] which were published for comment and which include several provisions that meet not only the FDAAA requirements but put in place further protections to protect the integrity of the Foundation's work. The bylaws provide for significant transparency around conflicts of interest issues, acceptance of donations and grants;

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[9] 21 U.S.C. § 379dd.

[10] Statement of Senator Kennedy (D-MA), 153 Cong. Rec. S11937 (Sept. 21, 2007).

[11] Statement of Senator Kennedy (D-MA), 153 Cong. Rec. S5759, S5764 (May 9, 2007).

[12] These requirements and other information are found in 21 U.S.C. § 379dd, unless specified otherwise.

[13] On November 16, 2007, FDA issued a press release announcing the names of the initial 14 appointed voting members of the Board. FDA News Release, "FDA Announces Board Members of Reagan-Udall Foundation," *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109029.htm.

[14] 74 Fed. Reg. 68,028 (Dec. 22, 2009).

and review of gifts.[15,16] The bylaws also set forth a separate, detailed policy in Appendix A, titled "Ethical Guidelines for Identifying and Managing Conflicts of Interest."[17] This policy requires, among other things, that the Foundation post on its website various information related to its conflicts of interest policies and decision-making. Moreover, the law requires that the Foundation and FDA conduct annual reviews of the Foundation's activities and submit reports to Congress, allowing for multiple levels of oversight. With these statutory protections, the Foundation's activities will remain objective and free of undue influence by any particular group.

Despite these efforts and protections Congress continues to block funding for the Foundation. The FY 2011 appropriation for FDA contained a prohibition against implementing the statutory provision that is the funding mechanism.[18] The Foundation has reportedly received some funds from private sources to work on a few projects.[19] Nonetheless, without the federal funds (and support) necessary to build an infrastructure, the Foundation will never become an operational organization. At present, the Foundation does not have a website, and a recent review of online sources did not permit identification of even basic information, such as a current list of the Board's voting members.

Notably, while Reagan-Udall's implementation continues to be stalled, European governments are lending strong support to the use of public-private partnerships to advance regulatory science. In 2007 (the same year Congress created the Foundation), the European Union and the European pharmaceutical industry association (EFPIA) established the Innovative Medicines Initiative (IMI), which is described as "Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients . . . [which] supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe."[20] A March 2011 press release indicates that the IMI has recently launched a second wave of research projects (focusing on areas including cancer, infectious disorders and electronic health), with a total of 23 current research projects and over €450 million (approximately USD $658 million at the time of publishing) committed by the European Commission and the EFPIA.[21]

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[15] *Id.* at 68,031.

[16] *Id.* at 68,034.

[17] *Id.* at 68,033-34.

[18] Alliance for a Stronger FDA Website, Funding for the Reagan-Udall Foundation (May 23, 2011), *available at* http://strengthenfda.org/2011/05/23/funding-for-the-reagan-udall-foundation/.

[19] For example, in March 2011 the Foundation received a grant from the Bill & Melinda Gates Foundation for the purpose of "accelerate[ing] the development of new TB drug regimens by testing drug candidates in combination before they are individually approved." Gates Foundation Website, *available at* http://www.gatesfoundation.org/Grants-2011/Pages/Reagan-Udall-Foundation-OPP1027026.aspx.

[20] Innovative Medicines Initiative (IMI) Website, *available at* http://www.imi.europa.eu/.

[21] On March 8, 2011, IMI issued a press release announcing new projects. IMI Press Release, "IMI announces a new total of 23 unique projects to boost drug innovation", *available at* http://www.imi.europa.eu/sites/default/files/uploads/documents/PRESS%20RELEASE%20IMI%20Press%20Briefing%208%20March%202011.pdf.

Two sister agencies of FDA, the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC), do have active Foundations to facilitate public-private partnerships. NIH has the Foundation for the NIH (FNIH), established by Congress in 1990. FNIH raises private funds and creates public-private partnerships to support the mission of NIH by combining the expertise and resources of NIH with those of industry, the public and philanthropic communities.[22] CDC has the CDC Foundation, which has provided $300 million since 1995 to help CDC pursue innovative ideas that need support from outside partners, launching more than 500 programs around the world and building a network of individuals and organizations committed to supporting CDC and public health. CDC Foundation partnerships help CDC launch new programs, expand existing programs that show promise, or establish a proof of concept through a pilot project before scaling it up.[23]

Proposal

Restore Funding for the Reagan-Udall Foundation: The Food and Drug Administration Amendments Act of 2007 (FDAAA) provides that FDA must transfer annually between $500K and $1.25 million to the Foundation for operations/administrative expenses. Congress should remove restrictions on FDA's ability to transfer federal funding to the Foundation as allowed by statute.

CREATE AN FDA "EXPERIMENTAL SPACE," LED BY A CHIEF INNOVATION OFFICER, TO PILOT PROMISING NEW SCIENTIFIC AND REGULATORY APPROACHES

Executive Summary

The Food and Drug Administration (FDA) has developed several initiatives to advance regulatory science. These include the FDA/NIH Joint Leadership Council[24], the academic Centers of Excellence in Regulatory Science, and FDA's Critical Path Initiative. However, FDA's ability to incorporate modern science into its regulatory processes has been limited because there is no entity within the agency with unified responsibility for systematically analyzing the findings and recommendations from these groups, and clear authority to pilot promising scientific and regulatory approaches. An FDA "Experimental Space," led by a new Chief Innovation Officer, should be established with the responsibility and authority to ensure that promising new scientific and regulatory approaches are integrated into agency operations at all levels.

Background

Currently, FDA's Office of the Chief Scientist is charged with coordinating internal and external outreach to identify critical regulatory science and innovation needs and developing a strategic plan for science at the FDA. The FDA has also established a high-level advisory board, the

[22] Foundation for the NIH Website, *available at* http://www.fnih.org/.

[23] CDC Foundation Website, *available at* http://www.cdcfoundation.org/who/story.

[24] FDA-NIH News Release, *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm201706.htm.

Science and Innovation Strategic Advisory Council, comprised of the Chief Scientist and representatives from the Office of the Commissioner, the various Centers, and the FDA Office of Regulatory Affairs. The Advisory Council meets twice a year to identify and communicate key scientific priorities from each center, to set and discuss major cross-cutting scientific priorities for the agency, and to propose and evaluate major programs and partnerships. The FDA also has an FDA Science Board that provides advice to the Commissioner, the Chief Scientist and the centers on complex scientific and technical issues within the agency, industry, and academia. The Board reviews the Science and Innovation Strategic Advisory Council's scientific plan and regulatory science priorities.

Within the Office of the Chief Scientific Officer is the Office of Science Innovation, which provides strategic leadership, coordination, infrastructure and support for innovation in FDA science that is intended to advance the Agency's ability to meet its mission to protect and promote public health. The Office of Science Innovation is theoretically charged with, among other things, supporting core scientific capacity and infrastructure within FDA, and fostering development and use of innovative technologies in product development and evaluation. This Office, however, lacks the statutory mandate to respond to external and internal recommendations by establishing specific pilot programs, and to implement successful programs into FDA's everyday regulatory decision making process.

Proposal

The Federal Food, Drug and Cosmetic Act (FFDCA) should be amended to establish an FDA "Experimental Space", led by a new Chief Innovation Officer, with the responsibility and authority to identify promising new scientific and regulatory approaches, with input from stakeholders inside and outside the agency, and ensure that these approaches are integrated into agency operations at all levels, and harmonized with the approaches of other mature regulatory agencies. Examples of such approaches might include the qualification of a particular biomarker, the acceptance of novel clinical trial design methodologies, incorporation of electronic health record technologies, alignment and rationalization of regulatory pathways for the approval of drugs/biologics and companion diagnostics, or adoption of novel methods in predictive toxicology.

Among the Chief Innovation Officer's duties should be the systematic analysis of the recommendations of all internal and external entities involved in advancing regulatory science, such as the FDA Science and Innovation Strategic Advisory Council, the FDA Science Board, the National Center for Toxicology Research, the FDA/NIH Joint Leadership Council, the Reagan-Udall Foundation, and key public-private partnerships such as the academic Centers of Excellence in Regulatory Science, the Biomarkers Consortium, the Patient Reported Outcomes Consortium (PROC), and the Predictive Safety Testing Consortium (PSTC).[25] Analyses should be published for public comment for at least 30 days.

[25] FDA, Existing Public Private Partnerships, *available at* http://www.fda.gov/AboutFDA/PartnershipsCollaborations/PublicPrivatePartnershipProgram/ucm166082.htm.

Further, the Chief Innovation Officer's responsibilities should include the development of implementation plans for pilot programs to incorporate recommendations from governmental, public/private organizations and academic regulatory science initiatives into agency regulatory decision making. Implementation plans should be published for public comment for at least 60 days prior to initiation of any pilot program.

Most importantly, the Chief Innovation Officer should have the authority, with input from Center representatives, to establish and oversee the implementation of pilot programs within the Centers, and ensure participation by cross-disciplinary pilot teams.

At least every two years, the Chief Innovation Officer should submit a report to Congress every two years detailing FDA's progress with respect to the integration of new scientific and regulatory approaches into agency operations, and explaining why any recommended approaches were not implemented.

ENHANCE FDA'S ACCESS TO EXTERNAL SCIENTIFIC AND MEDICAL EXPERTISE

Executive Summary

The Federal Food, Drug, and Cosmetic Act (FFDCA) establishes the Food and Drug Administration (FDA) as the preeminent agency charged with evaluating cutting edge science as it is applied to the prevention, diagnosis, and treatment of human disease. FDA has also been perceived by many as the global standard bearer for regulatory review of drug and biologic applications. However, scientific and medical knowledge, techniques, and technology are advancing at a more rapid pace today than at any other time, and FDA's capacity to access information about these advances has not kept pace. It is essential that FDA's access to scientific and medical advice be enhanced by improving the operations of FDA Advisory Committees, establishing Chief Medical Policy Officers in the immediate offices of the Center Directors and providing FDA staff with additional avenues for accessing external scientific and medical expertise.

Background

Improving the Operations of FDA Advisory Committees. FDA regularly looks to outside experts to provide the Agency with independent opinions and recommendations on a variety of complex medical and scientific issues, typically through the use of Advisory Committees. Federal Advisory Committees were initially established under the Federal Advisory Committee Act (FACA), which defines an advisory committee, in the broadest sense, as any committee, board, commission, or similar group of independent experts established or used by one or more federal agencies to obtain advice or recommendations.[26]

The FFDCA requires FDA to establish panels of independent experts (*i.e.,* Advisory Committees) for "the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug" or

[26] 5 U.S.C. App. 2, § 3(2)(C).

biologic.[27] Currently, there are approximately 20 standing Drug Advisory Committees. The activities of FDA Advisory Committees are subject to detailed requirements and procedures, set forth in 21 C.F.R. Part 14. As an example, any meeting of an FDA Advisory Committee must be announced in the *Federal Register* at least 15 days in advance of the meeting, except in very limited circumstances when authorized by the Commissioner of Food and Drugs.[28]

In recent times, FDA has found it more difficult to populate Advisory Committees with qualified members. This is in part due to the establishment of new conflict of interest requirements under the Food and Drug Administration Amendments Act of 2007 (Title VII), and FDA's interpretation of that statute. Over time (FY2008-FY2012) the new requirements progressively limit FDA's ability to grant waivers permitting individuals with essential expertise, but who also have a conflict of interest, to participate with respect to a particular matter before the committee. The waiver caps apply even though the type, nature, and magnitude of the individual's financial interests must be disclosed on FDA's website.

FDA Advisory Committees have historically used the most knowledgeable and highly qualified individuals to obtain the best available information. This authority is critical for reviews of the cutting-edge science and next generation innovation that is the bailiwick of biotechnology companies. In many cases, only a handful of qualified experts may exist to provide the agency with appropriate review of complex and technical issues surrounding new products. For example, for certain rare diseases areas or product categories, the universe of highly knowledgeable and qualified individuals may be quite small. In some circumstances, virtually the only experts in an area are individuals who are involved as advisors or participants in the research and development leading to the innovation being reviewed by FDA.

These individuals, who may have financial interest and thus a potential conflict, can be essential to a meaningful discussion of the issues surrounding review of a new product. Disqualifying them, or limiting their ability to meaningfully participate, could adversely impact the ability of an advisory committee to comprehensively evaluate a particular issue. Allowing such individuals to participate in an FDA advisory committee is vitally important because making decisions based on the best and most relevant science depends on the Agency's ability to seek and use the advice of these experts. Flexibility in the issuance of waivers is crucial to achieving this goal.

As with efforts to reduce private financing of research, policies that prohibit participation on advisory committees or impose other rigid standards contain a flawed, underlying assumption – that certain experts are necessarily biased simply because they work with industry. Basing national policy on that assumption undervalues the expertise and professional integrity of many of the scientists and researchers who participate in FDA deliberations.

The best way to achieve the twin goals of maintaining research integrity while promoting innovation is to enact policies that ensure maximum disclosure of possible conflicts as well as

[27] 21 U.S.C. § 355(n)(1).

[28] *Id.* § 14.20(a).

provide regulators or other oversight bodies the discretion to make case-by-case decisions. This has been the federal regulatory framework that has led to the discovery and development of hundreds of biotechnology products over the years.

In addition, patient groups and patient research foundations, are in a strong position to characterize benefit. They tend to have a broad understanding of the state of the patient population, and include individuals able to understand intimately the clinical benefits and risks of an approval. Such individuals should have a stronger role in Advisory Committee deliberations.

Providing FDA staff with additional avenues for accessing scientific and medical expertise. FDA also has the ability to utilize an external expert (a "consultant") or a group of external experts outside of the Advisory Committee process, including providing advice to FDA on particular drug applications. The following groups are *not* considered an Advisory Committee: (1) a "group of persons convened on an ad hoc basic to discuss a matter of current interest to FDA, but which has no continuing function or organization and does not involve substantial preparation;" and (2) a "group of two or more FDA consultants meeting with the agency on an ad hoc basis.[29] An internal CDER policy addressing clinical review procedures explains that FDA reviewers sometimes use information not contained in an application, including from "consultations with others outside the review team, such as internal or external consultants."[30] For example, the Agency will, at the request of a sponsor, engage in a "special protocol assessment" in order to assess whether a particular protocol is adequate to meet scientific and regulatory requirements.[31] In assessing a protocol under these procedures, FDA "can seek Advisory Committee review of a clinical protocol or can obtain advisory review from selected advisory committee members, special government employees, or other consultants."[32]

However, no adequate mechanism exists to ensure that FDA makes best and well-coordinated use of its ability to seek advice from external experts outside the Advisory Committee process. Such external experts could be invaluable in providing the agency with advice on broad (not product-specific) emerging medical and scientific issues, for example acceptance of surrogate endpoints in oncology, clinical trial design and post-market monitoring methods for medicines that may have rare but several adverse events, and appropriate benefit-risk balance for medicines to treat serious and life-threatening diseases.

Proposals

Fix FDA Advisory Committee policies to improve committee operations:

- Repeal financial conflict of interest waiver caps (while retaining appropriate disclosure requirements) to ensure that FDA has, and uses, significant discretion to grant financial

[29] *Id.* § 14.1(a)(5)(i), (ii).

[30] CDER Manual of Policies and Procedures (MAPP) 6010.3, Att. A, at 12-13 (effective Dec. 10, 2010).

[31] FDA, Guidance for Industry: Special Protocol Assessment, at 1-2 (May 2002).

[32] *Id.* at 8.

conflicts of interest waivers on a case-by-case basis for potential advisory committee members whose expertise is essential.

- Amend Section 505 of the FFDCA to include language requiring that committees considering the safety or effectiveness of drugs or biologics include at least one medical or scientific expert chosen by a patient group or research foundation whose interests are in the specific disease or diseases proposed to be treated by the drug or biologic under consideration. Such representatives would be in addition to any consumer representative already present on a given committee, and should be full voting members of that committee.

Create Chief Medical Policy Officers with responsibility for identifying and addressing broad medical and scientific policy disputes, and ensuring that FDA staff have access to the external expertise necessary to resolve those disputes: Create Chief Medical Policy Officers (CMPOs) within the immediate Offices of the Directors for the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). CMPOs would:

- work with review divisions to develop proactive and consistent strategies for the Centers to address emerging medical and scientific policy issues, including new peer learning and peer review mechanisms.
- be empowered to coordinate and improve reviewer access to external advice via advisory committees, working with the Office of Special Medical Programs[33] which currently has oversight of FDA Advisory Committees. For example, CMPOs could work to determine whether FDA is making the best and most efficient use of its Drug Advisory Committees. Among other things, a CMPO could examine whether the right type and number of issues are being referred to Advisory Committees, whether Advisory Committees have the necessary expertise to advise on the matters referred to them, and whether new Advisory Committees should be established at the FDA or Center level. In this connection, note that the FDA Science Board has recommended the establishment of Scientific Advisory Boards for each Center.
- be empowered to coordinate and improve reviewer access to external experts outside the advisory committee process. Such external experts would be Special Government Employees, and thus subject to conflict of interest and confidentiality requirements, and their findings would be made public. As appropriate, the CMPO and Review Divisions could hold public forums with presentations by industry, academia and patient organizations on key emerging scientific and medical issues.
- be charged to work closely with any new Chief Innovation Officer in the implementation of regulatory science pilot programs that impact on policy development.

[33] FDA Staff Manual Guides (SMG 1140.1), Office of Special Medical Programs (effective Aug. 7, 2009).

ENABLING MODERNIZED PATIENT-CENTRIC CLINICAL DEVELOPMENT

INCREASE ACCESS TO INNOVATIVE TREATMENTS AND THERAPIES THROUGH PROGRESSIVE APPROVAL

Executive Summary

Patients, industry, Congress, and others are eager to find ways to deliver safe and effective new drugs and biologics to patients. Patients, particularly those with illnesses for which no adequate therapy exists, want access to promising new therapies earlier in the drug development process. Smaller biopharmaceutical companies that develop those therapies are sometimes unable to maintain operations through extensive phase III testing without revenue from marketing of products. Expanding and improving the accelerated approval pathway into a progressive approval mechanism would provide patients timely access to needed therapies. This pathway would be limited to innovative products for unmet medical needs, significant advances to standard of care, targeted therapies, those that have been approved by the EU and other mature regulatory agencies. Additionally, this pathway would ensure risk-benefit analysis that incorporates the safety and needs of patients in the real world.

Background

The current new drug development and approval process is uncertain, lengthy, and expensive. It can take 10 to 15 years for a molecule in the earliest stages of development to be translated into a finished and approved drug product available for use by patients. The cost of developing an approved drug has been estimated between $800 million and $1 billion.

The current drug approval process and standards at the Food and Drug Administration (FDA) date to the early 1960s. Following preclinical work that provides an adequate assurance of safety for human testing, a drug's sponsor will typically conduct several phases of clinical trials that begin with small safety studies and conclude with large-scale controlled trials for clinical effectiveness. FDA regulations describe three phases of testing, but federal law does not require three phases. In fact some drugs have been approved on the basis of testing that combined two phases (Phase I/II or Phase II/III), and some have been approved on the basis of Phase II studies.

FDA then reviews each new drug application for proof of safety and effectiveness. The Federal Food, Drug, and Cosmetic Act (FFDCA) requires "substantial evidence" of the drug's effectiveness for its intended use, which is defined by statute to mean that "adequate and well-controlled investigations" demonstrate the drug will have the intended effect. When FDA finds a new drug safe and effective, it is essentially concluding that the drug's benefits outweigh its risks when the drug is used as described in the proposed labeling. This is in essence an exercise in risk/benefit balancing. A similar standard applies to biological drugs, which are the subject of a different type of application.

Federal law generally prohibits the distribution and marketing of new drugs prior to FDA approval. Patients, particularly those suffering from life-threatening or serious medical

conditions, have long sought access to drugs earlier in the drug development and approval process. Advocacy by HIV/AIDS patients in the 1980s led to the accelerated approval scheme, and advocacy by terminally ill patients in the 1990s led to improvements in compassionate use programs while drugs remain investigational.

First, FDA may grant accelerated approval to new drugs for serious or life-threatening diseases that represent a meaningful therapeutic benefit over existing treatment. The agency may approve such a drug on the basis of a surrogate endpoint "reasonably likely" to predict clinical benefit or another clinical endpoint other than survival or irreversible morbidity. Surrogate endpoints are markers, such as tumor shrinkage or CD4 cell counts, used in clinical trials as an indirect measurement of a clinical outcome, such as patient survival. The use of surrogate endpoints permits approval earlier than the use of clinical endpoints. The sponsor of a drug approved under the accelerated approval pathway must perform adequate and well-controlled clinical trials after approval, to verify the anticipated clinical benefit of the therapy.

Second, under its expanded access regulations, FDA permits the use of an investigational drug for treatment of patients with "immediately life-threatening" or "serious" medical conditions when there is no comparable or satisfactory alternative treatment as well as during an emergency. FDA grants expanded access for patient groups of varying sizes, depending on the state of the evidence on safety and effectiveness.

Accelerated approval and expanded access, while helpful, are narrow in their scope. In fact, most patients do not benefit from them. These pathways do not provide subpopulations of patients access to promising therapies that may help them. For example, cancer patients identified using a biomarker, for which targeted drug therapy has been shown effective, would not receive early access to the therapy under any existing program. Terminally ill patients do not receive early access to promising therapies, despite the fact that the risks they face from the disease may far outweigh risks they face from taking the drug. Accelerated approval only applies to a subset of drugs that have the potential to treat serious diseases; thus, fewer drugs are made available via that pathway. Last, no existing program provides a method for companies to fund continued research of a promising drug. As a result, promising drugs may never be made available to patients because companies do not have the resources to continue developing the drug.

Stakeholders and thought leaders have repeatedly suggested that FDA implement, or Congress enact, some sort of "progressive approval" mechanism for promising new therapies to provide earlier access to patients that need them. Progressive approval is not a novel idea. Congress created a progressive approval pathway for some animal drugs in 2004, and the European Commission (EC) also progressively approves some human drugs.

The EC will progressively approve a drug that (1) targets a seriously debilitating or life-threatening disease, (2) can be used in emergency situations, in response to public health threats, or (3) is a designated orphan drug. The drug is approved before all of the relevant safety and effectiveness data are available, subject to the condition that the sponsor meet "specific obligations." These include conducting confirmatory clinical trials within an agreed upon timeframe. The progressive marketing authorizations are valid for one year, on a renewable

basis. The European Medicines Agency (EMA) assesses each renewal application to determine whether the company will be able to confirm the positive risk/benefit profile of the drug. The EMA considers whether the "specific obligations" associated with the progressive marketing authorization must be modified or whether they have been completed. Once the specific obligations are fulfilled, the EC may fully authorize the drug at any time.

Proposal

Eligibility. Progressive approval should be available for a new drug intended to provide a meaningful advancement in the treatment of serious or life-threatening disease, which offers the promise of one or more of the following:

- first approved therapy for a condition or targeted subpopulation with the condition
- ability to treat patients unresponsive to, or intolerant of, existing approved therapies
- ability to treat rare diseases or disease subpopulations based on biomarkers or genetics (*e.g.,* personalized medicine)
- ability to offer a significant improvement in outcomes for patients compared to existing approved therapies, either alone or in combination with existing approved therapies. Improvement in outcomes may reflect improved efficacy, improved safety, or an enhanced balance of efficacy and safety, compared to existing approved therapies and products that have been approved by the EU and other mature regulatory agencies

The relative risk/benefit profile of these drugs is different from other drugs, which justifies their earlier availability to patients (subject to appropriate controls and additional data gathering). For purposes of determining whether a new drug offers the promise of meaningful advance over existing approved therapies, only therapies with full FDA approval should be considered as existing approved therapies (*e.g.*, drugs available under the Progressive Approval or Accelerated Approval pathways should not be considered as existing approved therapies).

Process for Eligibility and Designation Decisions. The sponsor could apply at, or any time after, a pre-IND meeting. Whether a drug should be considered for, or the subject of, progressive approval can be recommended by FDA, but should be the option of the sponsor. FDA should issue, upon request within 60 calendar days, a written determination explaining whether a drug and a proposed indication is, or is not, eligible for progressive approval. FDA's written determination should include an explanation of the rationale for FDA's decision. FDA's determination should be publicly available at the time the decision is made, but the sponsor can request that the final decision not be disclosed (prior to approval of the product) due to concerns regarding disclosure of proprietary information about product development plans. A decision that the product is not eligible for progressive approval should not preclude a subsequent decision (based on new information) that the product is eligible for progressive approval. There should be no requirement to seek, or obtain, an eligibility determination prior to applying for progressive approval. Products that are under IND at the time of the introduction of this progressive approval pathway, shall maintain the option, at the election of the sponsor, of pursuing approval through the existing accelerated approval pathway or through the progressive approval pathway.

Appeal Rights (Adverse Designation Decisions). In the event of an adverse decision on the progressive approval application, an applicant can invoke a statutory administrative appeal process that includes (at the applicant's option) stakeholder (public) and expert input. The FDA should provide a response to an appeal within 60 calendar days. If FDA issues an adverse appeal decision, the agency should explain what would be needed to satisfy the standard.

Standard for Progressive Approval. Progressive approval should be granted:

- In general, at the earliest possible time when the available evidence suggests that the drug is more likely than not to provide a favorable benefit-risk tradeoff to its intended patient population
    - For example, progressive approval may typically be granted following completion of one Phase II trial, provided that the available evidence suggests a favorable benefit-risk tradeoff
    - May also be granted earlier, at the Commissioner's discretion, if the Commissioner concludes that the benefits of immediate availability of the drug outweigh its risks for the intended population
- If necessary to create the conditions whereby the drug is more likely than not to provide a favorable benefit-risk balance, FDA should use all available tools, including REMS, post-market surveillance, controlled distribution, physician training and registries, etc.

Approval should be conditioned on written agreement between FDA and the sponsor regarding further development plans designed to lead to the submission of a supplement for full approval under section 505 of the FFDCA, or 351 of the PHSA, within a period of time to be negotiated on a case-by-case basis. FDA should also have the authority to waive the requirement to obtain full approval, if it finds that the data necessary to satisfy the standard in question cannot be collected, for example due to ethical concerns or scientific limitations (referred to as "exceptional approval").

Expiration and Renewal. Progressive Approval should remain in effect unless and until FDA determines that the conditions for Progressive Approval (*i.e.*, that the available evidence suggests that the drug is more likely than not to provide a favorable benefit-risk balance) no longer apply, as described below under "Withdrawal of Approval"). The holders of NDAs and BLAs approved via progressive approval should submit supplements to convert their products to full approval when they have gathered the data needed for that approval.

Postmarket Restrictions. Same post-marketing reporting requirements as drugs approved under the traditional approval process (*i.e.*, recordkeeping and safety reporting). FDA may use all available tools, including REMS, post-market surveillance, controlled distribution, physician training and registries, etc. to ensure a favorable benefit-risk balance in the post-market.

Withdrawal of Approval.

- Withdrawal of approval (with an opportunity for a post-withdrawal hearing) should be available in the event the Commissioner concludes that it is no longer more likely than not that the benefits of the product outweigh its risks.
- Sponsor will be required to submit a report to the FDA once every two years, until full approval is obtained or progressive approval is revoked. This report will provide

an update on the progress of the agreed development program toward full approval; and will update all available evidence regarding the efficacy and safety of the drug in the approved indication and population; and will provide an updated assessment of the benefit-risk balance based on all available evidence at that time

- Following submission of each such report, FDA will conduct a review of the product's Progressive Approval status. The FDA may convene an Advisory Committee in conjunction with such review. If the Commissioner concludes that it is no longer more likely than not that the benefits of the product outweigh its risks in the intended population, then the FDA may initiate withdrawal procedures.
- FDA should utilize all available tools in order to maintain a favorable benefit-risk balance, including labeling changes, REMS, etc., prior to withdrawing Progressive Approval
- If FDA determines to withdraw Progressive Approval status, the sponsor should be notified of the FDA's assessment, in writing. FDA's written assessment of the benefit-risk balance should be made publicly available.
- The sponsor should be entitled to appeal the FDA's decision to withdraw Progressive Approval status.
- Prior to ruling on an appeal, the FDA should convene an Advisory Committee, if it has not already done so in conjunction with its original withdrawal assessment.
- The appeal process should be completed within [180 days]
- The product should retain its Progressive Approval status and remain commercially available until final resolution of the appeal process.

Labeling and Promotion. The package insert of a progressively approved (or exceptionally approved) drug should disclose its status. Marketing and promotional claims should be permitted, in accordance with the product label, in the same manner as with drugs granted full approval.

Charging and Reimbursement. Drugs approved under this pathway are not considered investigational drugs, thus, are subject to the same coverage and reimbursement policies applicable to drugs approved under the traditional process.

Generics and Biosimilars. Once full / traditional approval has been obtained, the drug may be a reference product for purposes of generic or biosimilar drug approval. A regular period of data exclusivity will apply at that point (and protect the data just submitted for the full approval).

EMPOWER FDA TO UTILIZE A WEIGHT-OF-EVIDENCE APPROACH

Executive Summary

The Federal Food, Drug, and Cosmetic Act (FFDCA) requires that the Food and Drug Administration (FDA) approve applications for new drugs when they have been demonstrated to be safe and effective under the intended conditions of use. Under Section 505(d), effectiveness is established when FDA is satisfied that there is "substantial evidence" that the new drug has the intended effect that it is purported to have. FDA typically requires two "adequate and well controlled" studies under this standard. A weight of evidence approach to data analysis,

however, allows the decision-maker to look at all data and information, whatever its value, and give each appropriate consideration.

Background

FFDCA grants FDA significant latitude in defining the contours of the studies establishing "substantial evidence". Statistical significance is generally demonstrated by meeting the standard of $p < 0.05$ with respect to pre-determined endpoints.[34] This means that there is a less than one in twenty chance that the observed difference between test articles (*e.g.*, an investigational drug and placebo) is "just" a product of random variability within a data set. Said differently, if there truly was no difference and the same experiments were conducted twenty times, we would expect to falsely "find" a difference just once.

Ultimately, however, the $p < 0.05$ standard for statistical significance is an arbitrary one. Observations that clearly have practical meaning may fall short of statistical significance due to the statistical power of a given study. For example, if one drug in a given class demonstrates effectiveness with a *p* value of 0.04 after a very large clinical trial, and a second drug within the same class – and as to which all scientific principles suggest would act similarly – demonstrates effectiveness with a *p* value of 0.06 after a smaller study, it would not make good sense to say that the first is effective whereas the second is not. It would also be an inefficient use of resources (and potentially unethical) to force the sponsor of the second drug to recruit additional subjects when the result of doing so, lowering the *p* value to reach 0.05, is more or less a foregone conclusion.

Data analysis may also show that a statistical significance exists when such significance has no meaning in practice. For example, a clinical study for a topical antibiotic ointment may show that individuals given the treatment, as opposed to placebo, had a small, but statistically significant increase in the development of gastric ulcers. Given that there is no reason to expect that local, topical application of an antibiotic would have any causal relationship to ulcers, it should be unnecessary to conduct a full follow-up study to demonstrate the lack of such a relationship, particularly when other similar medications are already known not to have such an effect. In each of these cases, the statistical analysis fails in that it becomes divorced from basic first principles of science.

A weight of evidence approach to data analysis, on the other hand, would allow a reviewer to consider a study whose data demonstrate a statistical *p* value that, while not technically meeting a standard definition of "significance", nonetheless provides evidence of safety or effectiveness. When reviewing an individual set of data and the question of causation, the reviewer would look

[34] The measure of statistical significance being at the 5% level is more or less an artifact of historical chance, when full statistical tables were difficult to manually produce. As a result, Ronald A. Fisher's seminal 1925 text on the subject, although providing tables with multiple levels of significance for other values, only provided the 5% level for one particular table. This value subsequently became the standard of significance for the biological and medical sciences. See Stephen Stigler, Fisher and the 5% Level, 21 CHANCE 12 (2008).

at the strength of the association (the statistical analysis) in the context of the data's internal consistency as well as its coherence with first principles of science.[35]

Such an approach to data analysis is not new to FDA or to other governmental agencies. The Environmental Protection Agency regularly utilizes a weight of evidence approach to determining acceptable levels of various substances in drinking water and the atmosphere. FDA also regularly invokes the weight of evidence concept when communicating issues of causation; for example, when considering the toxicity of a regulated product or a qualified health claim for a food. In a 2009 briefing on the status of FDA regulatory science, the agency stated that regulatory and public health decisions promulgated by the FDA are based upon the weight of scientific evidence. Nonetheless, FDA rarely articulates what it means when it says "weight of evidence." Conducting a weight of evidence evaluation requires scientific expertise and judgment, but it enables regulatory decision makers to consider and give weight to a broader range of data, including information that might otherwise fail the traditional, yet somewhat arbitrary, definitions of statistical significance.

Proposal

The last sentence of FFDCA Section 505(d) should be amended to state that if the Secretary determines either, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation), or that the overall weight of the evidence (including all relevant scientific data and information not otherwise prohibited from reliance or reference by the agency) is sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence.

LEVERAGE ELECTRONIC HEALTH RECORDS TO FACILITATE CLINICAL RESEARCH

Executive Summary

Every new drug's sponsor spends years designing and conducting clinical trials to show the drug is safe and effective. Using health information technology (IT) such as electronic health records (EHRs) in clinical research will improve and speed up the drug development process, and decrease costs. However there are significant barriers preventing wide-spread use of health IT in clinical research, including slow adoption by providers, and lack of standards development. FDA can help remove those barriers. Congress should create a Clinical Informatics Coordinator in the Office of the Commissioner of Food and Drugs charged with developing processes to validate and encourage the use of health IT in clinical research, and establishing pilot projects to use health IT in clinical research.

Background

[35] It is important to note that such an approach does not abandon statistical analysis, but rather borrows from the Bradford Hill criteria for causation when considering the question of whether the data are indicative of real differences.

Health IT can improve the quality, and efficiency, of the health care system. Congress has passed legislation promoting the use of health IT by encouraging the adoption of electronic health records to reduce medical errors, reduce health care costs, and improve health care quality. The widespread adoption of interoperable EHRs can facilitate the secure exchange of electronic health information, which can be used to speed the drug development process by improving the efficiency of clinical research.

To develop a new therapy for use by patients, companies spend the majority of the drug development phase conducting clinical trials to demonstrate that the drug is safe and effective. The clinical trials generally proceed in three phases, beginning with smaller studies to gather preliminary safety information about the drug, followed by larger studies to gather information about safety and effectiveness. This process can take six to seven years. EHRs can be used to improve how clinical research is conducted.

Specifically, EHRs can help companies more effectively identify, recruit, and enroll patients for clinical trials. Companies often face challenges recruiting subjects to participate in clinical trials studying drugs for a rare disease or for trials that require a large number of patients. Difficulty recruiting eligible subjects increases the time (and cost) to develop a drug. But electronic health records can be used to notify a physician if a patient is eligible for a clinical trial. This functionality will allow clinical trial investigators to more efficiently identify potential study participants eligible to participate in a trial.

Sponsors can also use health IT to better inform clinical study design. Data from EHRs can allow companies to simulate different clinical research models to determine the most efficient study design to assess the safety and effectiveness of a drug. Using health IT, sponsors can better understand the physiology of the target disease, the pharmacology of the drug compound to be tested, and the statistical methods that will be used to analyze the clinical trial results. This information can be used in designing the trial, which may improve the chance of clinical trial success.

Further, health IT can be used to more efficiently collect study data. Sponsors can eliminate redundant and time-consuming manual data entry by using EHRs to automatically populate case report forms.

Health IT can also allow investigators to protect subjects enrolled in a clinical trial by more effectively monitoring for adverse events. Sponsors can enroll patients in an electronic registry that allows the sponsor to track the patient's experience with the drug in real-time, relying on information contained in the patient's EHR. As a result, safety signals may be detected and addressed more rapidly, helping to ensure patient safety.

Despite the vast potential for improving clinical research through the use of health IT, significant barriers remain. Although Congress has provided funding to encourage the adoption of EHRs, the use of EHRs in clinical practice remains relatively low at this time. Work must be done to ensure interoperable standards and the secure exchange of data. In addition, validation methods for clinical research health IT tools are needed. But most importantly, FDA must issue standards governing activity in this area. Companies are less likely to use different approaches to clinical

trial research, even if those methods lead to more efficiency and better protections for clinical subjects, if FDA is unwilling, or unprepared, to apply data generated in clinical research using health IT in drug approval decisions.

Proposal

The Federal Food, Drug, and Cosmetic Act (FFDCA) should be amended to provide that the Commissioner of Food and Drugs appoint, within the Office of the Commissioner, a Clinical Informatics Coordinator. The Clinical Informatics Coordinator should develop a process to validate the use of health IT in clinical research and encourage the use of new health information technologies in clinical research protocols. FFDCA should also require that the Clinical Informatics Coordinator establish pilot projects to explore and evaluate the methods of incorporating emerging health IT to make the clinical research process more efficient. Not later than one year after the conclusion of the pilot programs, FDA should issue guidance for the conduct of clinical trials incorporating health information technology. The guidance should explain how FDA will evaluate such information when reviewing medical product applications.

REQUIRE FDA TO DISCLOSE TO THE SPONSOR REASONS FOR NON-APPROVAL

Executive Summary

The Federal Food, Drug, and Cosmetic Act (FFDCA) implies that licensing or approval applications are a binary question – approve or deny – due to phased, investigational review of applications; however, there is in practice a third response. In this case, the Food and Drug Administration (FDA) neither approves nor officially denies the application (which would require FDA to give the sponsor specific procedural rights such as a hearing), rather it finds the application to be incomplete in some way that makes the application ineligible for approval. When FDA makes such a finding, it should communicate to sponsors in clear terms why risk was determined to outweigh benefits and why authorities such as Risk Mitigation and Evaluation Strategies (REMS) – which are designed to mitigate risk – are insufficient (in addition to indicating what must be done to address any deficiencies). Such an approach would help create a consistent and transparent evaluation of risk-benefit, and provide the sponsor with better information on what, if any, additional studies are required to achieve approval.

Background

FDA, like most regulatory agencies, tends to be relatively risk-averse – there is a gravitational pull toward issuing a request for additional data when faced with data that does not clearly and greatly exceed the approval standards for safety and effectiveness. FDA has, however, been given the authority to implement a number of strategies to mitigate potential risks associated with the use of a given product. The first and least restrictive way is to limit the approved conditions of use. Here FDA can effectively exclude certain higher risk use scenarios without being forced to deny an application. Second, FDA can include warnings, and even black box warnings, to expressly contraindicate a treatment under certain high risk uses. Third, under the FDA Amendments Act of 2007, FDA can require the implementation of a REMS to manage a known or potential serious risk associated with a drug or biological product and ensure that the benefits of a drug or biological product outweigh the risks of that product when prescribed. In

each case, these mechanisms can be utilized to manage risk, and thereby alter the benefit-risk analysis.

Proposal

Section 505 of FFDCA should be amended to include a requirement that when the Secretary has determined that submitted Phase 3 clinical investigations are inadequate to support approval or the application otherwise results in the Secretary denying approval, sponsors of applications under this section or section 351 of the Public Health Service Act shall be provided with a written explanation as to the reasons for that conclusion. That document should include detailed justifications for why FDA believes that (a) label warnings, (b) a REMS (including each possible REMS element to assure safe use), or (c) post-approval research, are inadequate to ensure that the benefits of an approval outweigh the risks.

ATTACHMENT IV: FOOD & AGRICULTURE PROPOSALS

THE ROAD TO A BRIGHTER FUTURE FOR AGRICULTURAL BIOTECHNOLOGY

For the past two decades, the United States has played a leadership role in agricultural biotechnology innovation, contributing billions of dollars to the U.S. GDP. Unfortunately, the U.S. regulatory system for plant and animal biotechnology, which was designed in the mid-1980s to facilitate product development, is fast becoming an impediment to the development and commercialization of safe, beneficial products. Today, developers of agricultural biotechnology are less certain about the length and scope of federal regulatory approvals and the susceptibility of approvals to legal challenge. Greater certainty is needed to drive scientific innovation and reassure international trading partners, which is essential to U.S. producers of genetically-engineered products.

PROPOSED LEGISLATION

While the underlying statutory authorities and regulatory framework for agricultural biotechnology are sound, to improve the process, Congress can provide direction to the federal agencies responsible for implementing the governing statutes that most directly impact genetically-engineered plants and animals.

SENSE OF CONGRESS:

A. Congress recognizes the important role that biotechnology innovation has played the past 15 years in:

* improving the environment by reducing soil erosion, improving soil health, reducing consumption of fuel for farming equipment, allowing for the return of beneficial wildlife around farm fields, and less chemical runoff;

* helping U.S. growers' competitiveness in an increasingly competitive global market;

* creating jobs and stimulating economic growth; and

* maintaining healthy rural economies.

B. Congress acknowledges that science and the history of safe use have shown biotechnology crops to be safe for human health and the environment. As such, existing and future biotechnology products have the potential to make a significant contribution to the major challenges facing society: feeding, fueling and clothing the world's growing population in a manner that is sustainable.

C. Congress recognizes the importance of this technology to the national interest, including energy security, trade, competitiveness, food security, environmental protection and sustainability.

D. Congress directs that USDA and EPA consider the benefits of technological innovation in agriculture in achieving the goal of environmental protection and stewardship in carrying out their statutory authorities and complying with environmental statutes.

E. Congress affirms that regulatory decisions should be consistent with the World Trade Organization Agreement on the Application of Sanitary and Phytosanitary Measures and that regulatory decisions for agricultural biotechnology products shall be based on science and not socio-economic issues or the so-called "precautionary principle."

F. Congress reasserts the fundamental principles that guided the early development of the U.S. regulatory system: a) risk depends on the product and not the process by which it was produced; b) the extent and type of regulatory oversight should be commensurate with the relative safety of the product.

G. Congress affirms the Coordinated Framework for the Regulation of Biotechnology as the basis for regulation of agriculture biotechnology.

H. Congress supports regulatory agencies, which oversee biotechnology products, having sufficient resources and funding to perform their review in an effective and efficient manner.

I. Congress urges the creation of educational initiatives to improve the understanding of students in grades K-12 of basic elements of biotechnology, including agricultural biotechnology, and enhance their ability to pursue higher education and careers in the biological sciences.

J. Congress supports funding to the National Institute for Food and Agriculture and its programs to conduct further research in biotechnology.

CONGRESS DIRECTS THE SECRETARIES OF AGRICULTURE AND HEALTH AND HUMAN SERVICES, AND THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY:

A. To recognize the division of authorities as established in the Coordinated Framework and to eliminate and avoid unnecessary duplication of regulation.

B. To maximize agency resources by increasing the efficiency and effectiveness of the regulatory process, particularly for familiar products; providing greater predictability in data requirements, timeliness and decision making; and improving review and authorization timelines.

C. To take administrative actions designed to reinforce plant, animal and human safety and sound science as the sole basis for decision making; to endorse a history of safe use as an appropriate basis for regulatory reform; and to emphasize product over process as basis for regulatory jurisdiction and action.

D. To promptly submit a joint report to Congress on how each agency will accomplish these objectives.

CONGRESS DIRECTS THE SECRETARY OF AGRICULTURE:

A. To meet timeframes for decisions as reflected in regulations.

B. To provide support for maintenance of germplasm banks as a biodiversity resource.

C. To provide financial support for developing and commercializing biotechnology-derived minor use crops and commodity crops with value-added traits to benefit small farmers.

CONGRESS DIRECTS THE SECRETARY OF HEALTH AND HUMAN SERVICES:

A. To appoint experts in the field of genetically-engineered animals to Veterinary Medical Advisory Committees when genetically engineered animals are being reviewed as a result of a new animal drug application;

B. To permit interactions between FDA staff and Veterinary Medical Advisory Committee (VMAC) members to: 1) clarify data and questions during meetings of the VMAC when reviewing genetically engineered animals as a new animal drug; and 2) guide VMAC processes to ensure discussions stay on track.

C. To support small business innovation by continuing small business exemptions under the Animal Drug Use Fees Act.

CONGRESS DIRECTS THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY:

A. To maintain the Agency's long-standing policy of utilizing FIFRA Section 25(b) to avoid duplication of regulatory requirements for those plants and other macro organisms, seeds, and other plant parts that are already subject to regulation under the Plant Protection Act of 2000 and other statutes administered by the Secretary of Agriculture.

B. To ensure that the recordkeeping, reporting, data, and other requirements for plant-incorporated protectants and other biological products are based solely on considerations of safety and sound science and that the requirements traditionally required for chemical pesticides are not automatically applied to these biological products.

CONGRESS DIRECTS THE U.S. TRADE REPRESENTATIVE WITH SUPPORT FROM THE SECRETARIES OF AGRICULTURE AND HEALTH AND HUMAN SERVICES AND THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY:

A. To negotiate trade agreements with key U.S. export markets on: a) adoption of low level presence policies consistent with Codex guidance to advance trade in products authorized in the United States; b) minimizing/eliminating barriers to wood trade related to certification schemes that prohibit wood from genetically engineered trees; c) minimizing/eliminating barriers to cloning and genetically engineered animals and plants.

STATE OF NORTH CAROLINA
OFFICE OF THE GOVERNOR
20301 MAIL SERVICE CENTER • RALEIGH, NC 27699-0301

BEVERLY EAVES PERDUE
GOVERNOR

December 6, 2011

To the White House Office of Science & Technology Policy:

Twenty-seven years ago, North Carolina made a commitment to invest in the life sciences and, by embracing technology-based economic development, we tapped the best of our considerable wellspring of academic, commercial and workforce-training creativity. Our collective vision helped to establish North Carolina as a consistent leader among America's key life-science states and gave us a solid economic growth sector that actually added jobs during the recent recession. Those of us fortunate enough to be among the "elder states" on America's life-science map can contribute real and useful ideas to what will ultimately be a National Bioeconomy Blueprint.

In this document, we have shared specific solutions in each broad area of President Obama's request for information on the bioeconomy. I believe that, with additional time and money, solutions that have proven worthwhile in North Carolina can lift all boats, creating jobs across the nation. A combination of proven strategies and new ideas will help us tackle unfolding problems, from gaps in capital allocation to corrections in critically short supplies of some therapeutics.

The bioeconomy is broad and deep, and includes agriculture, marine science and energy, as well as therapeutics and diagnostics. It opens doors for this and future generations of Americans to prosper, and promises to help boost the health and well-being of our friends around the world.

Sincerely,

Beverly Eaves Perdue

NORTH CAROLINA BIOTECHNOLOGY CENTER

National Bioeconomy Challenge Response

Introduction

Forty years ago, scientists developed techniques that later allowed us to make human insulin. At the time, North Carolina's economy revolved around tobacco, textiles and furniture.

The discovery paralleled another change. Technology made us more efficient. Machines replaced human labor. Unskilled jobs went overseas. In the subsequent decades the South lost a significant number of jobs in its traditional industries. North Carolina was no exception. From 1996 to 2006 employment statewide dropped:

- 10 percent in furniture
- 23.5 percent in tobacco
- 51 percent in traditional textiles

North Carolina leaders looked through the job loss and saw opportunity. The state launched two centers in the early 1980s: the North Carolina Microelectronics Center to develop the information technology industry and the North Carolina Biotechnology Center to develop the life-science industry.

In the last three decades, the Biotechnology Center's work mirrors the intent of the Bioeconomy Challenge – working at all points along the technology development continuum to bridge gaps between research, business and education in order to create jobs. Through deliberate attention to this emerging industry, North Carolina built a **$64.6 billion** economic engine that supports more than **226,000 jobs**. Nearly 60,000 of those jobs are at life-science companies and pay nearly double the state's average private-sector wage.

These impacts didn't come through short-term investments or luck. North Carolina deliberately assembled the pieces to build its biotechnology cluster. Thousands of respondents to President Obama's request for information on the bioeconomy will offer ideas for initiatives that will work with increased federal funding. We want to share some ideas that proved valuable during the 27 years that North Carolina has nurtured this significant life-science growth engine.

E. Norris Tolson
President and CEO
North Carolina Biotechnology Center

NOVARTIS

FUJIFILM DIOSYNTH BIOTECHNOLOGIES

Research and Development

Life-science research faces major challenges that go beyond the technical: expensive infrastructure; complex research problems that involve multiple fields; and weak connections between research, invention and commercialization.

North Carolina designed programs to address each of these issues. Biotechnology Center grants strengthen infrastructure by putting research equipment in spaces accessible to multiple labs. Our grants fund multidisciplinary research teams to work on complex problems. And, to link academic research to commercialization, the Biotechnology Center funds projects of commercial interest. Junior scientists often work on those projects thereby broadening their future career prospects.

Partners

North Carolina's public and private universities; RTI International and other private research organizations.

Future Challenge

New ideas are required for job growth. In life science, discovery is expensive and proving ideas takes time. To meet this challenge, the federal government can:

- Increase funding to the level needed to stimulate life-science research and innovation long-term.
- Strengthen existing programs that fund proof-of-concept studies and intellectual property creation.
- Develop new funding programs that foster academic-industry collaboration and professional career transitions between academia and industry, such as industry post-doctoral fellowships.

Moving Life Sciences Breakthroughs from Lab to Market

Early-stage funding is the greatest challenge facing companies and universities commercializing technologies, according to a 2010 survey of North Carolina's life-science industry[1]. In the past decade, venture capital funding has declined substantially and life-science VC investments are now mostly focused on later-stage companies.

The Biotechnology Center created several funding programs to address this gap. The Technology Enhancement Grant helps universities strengthen a technology's ability to be licensed. Low-interest loans spur start-up, product development and growth for promising companies with few funding options. Finally, North Carolina allocated part of the state's pension fund to create the N.C. Innovation Fund that invests in innovative North Carolina companies and in other life-science investment funds.

Partners

State of North Carolina, Council for Entrepreneurial Development, Small Business and Technology Development Center, North Carolina's public and private universities, North Carolina angel and venture capital funds.

Future Challenge

Too little seed-stage risk capital is available for advancing promising technologies. To meet this challenge, the federal government can:

[1] Bridging the Gaps. *http://www.ncbiotech.org/business-commercialization/business-loans-support*

Areas of Future Promise

The techniques of biotechnology are widely applicable to a number of industries.

Agriculture
From food to fuel, or medicine to clothing, nearly anything that's not metal or glass can be produced in or by plants. Research, production and distribution jobs will abound.
More on the web at *ncbiotech.org/agbio*

Regenerative Medicine
Science fiction has become life-saving reality, as human organs grown from a patient's own cells are being produced in the laboratory and implanted in the patient.
More on the web at *wakehealth.edu/WFIRM*

Industrial and Environmental Applications
From engineering more efficient processes for industry to mitigating pollution, biotechnology is making a positive impact for the environment.
More on the web at *bio.org/content/new-biotech-tools-cleaner-environment*

BACKGROUND IMAGE COURTESY OF RTI


NCSU/BTEC


GRIFOLS

- Reduce uncertainty within the regulatory environment, a primary cause of diminishing venture investment in early-stage companies.
- Fill the gap by developing or expanding bridge funding programs that stimulate translational activities or refine a technology to make it more attractive to investors. Two excellent existing models are the National Cancer Institute's SBIR Phase II Bridge Award and the Department of Defense Commercialization Pilot Program.

Workforce Development

To compete in today's global economy, bioscience companies need employees with scientific competence and professional skills. Potential workers don't know where to get these skills.

North Carolina developed NCBioImpact[2], a public-private partnership of industry, universities, community colleges, and government, to educate employees for the biomanufacturing sector. This consortium has earned international recognition and enhanced the state's ability to recruit new manufacturing facilities. The resulting community of highly trained graduates and industry veterans enables North Carolina's biomanufacturing companies to fill more than 90 percent of job openings with local candidates.

Partners

Bio- and pharmaceutical manufacturers, North Carolina Biosciences Organization, University of North Carolina System, North Carolina Community College System, state and local governments.

Future Challenge

Success in other sectors and high-tech industries requires systemic changes to create a knowledgeable and "work-ready" employment base. To achieve this, classrooms from community college to graduate school must be more like the workplace. To meet these challenges, the federal government can:

- Engage students' imagination in K-12 Science, Technology, Engineering and Math (STEM) subjects through web-based technologies, including video games.
- Implement programs for high schools that enable students to earn a high school diploma and an associate's degree in five years.
- Involve industry advisory boards to develop and fund science education grant programs that use job-related success measures.
- Support professional science master's and doctoral programs that combine post-graduate work in science with industry sector-focused basic business education.

Regulatory

We live in a world replete with regulations. Consumers, companies and investors rely on clear, dependable and evenly enforced rules. In recent years the approval of medicines and medical devices has become increasingly unpredictable. N.C. life-science companies reinforce the message that the regulatory pathway is a significant challenge because it it is not clear when a product might be approved. This ambiguity further limits companies from recruiting investors to fund product development. An uncertain regulatory environment is undermining the innovation process and will lead to lost jobs if not handled well and soon.

Partners

North Carolina Biosciences Organization, state and local governments, industry, consumer groups, general public.

Future Challenge

The Biotechnology Industry Organization (BIO) drafted a five-year plan that suggests creating a 21st Century FDA. We support BIO's recommendations on the FDA. The federal government can also:

- Create a task force that includes the FDA, industry and consumer group representatives to develop recommendations for streamlining FDA approval processes while maintaining reasonable safety standards.
- Keep the 12 years of data exclusivity included in the biosimilars legislation passed under the Affordable Care Act. The protection is critical to continued innovation in investments in researching and developing new treatments for patients.

[2] *ncbioimpact.org*

DSM

Public-Private Partnerships

When North Carolina's leaders began building a biotech industry for the state, they drew on broad talents across the state. Experts and leaders in research, public policy, business development and worker training created initiatives that drove the new industry. Collaboration continues today, as demonstrated in this document.

The North Carolina Research Campus[3] in Kannapolis is a striking example of partnership. Where an old textile mill once stood is now home to state-of-the-art research facilities. Scientists from eight companies including LabCorp, Monsanto, and Dole as well as from seven public North Carolina universities and Duke University work side-by-side to better understand links between agriculture, nutrition and health.

Another example of partnership is the Centers of Innovation[4] program created by the Biotechnology Center. Here, broadly based public-private partnerships are established through industry-sector-focused commercialization centers. Current Centers of Innovation have been established to smooth the path from university lab to market in the areas of nanobiotechnology, advanced medical technologies, drug discovery and marine biotechnology.

Future Challenge

Limited funding for new discoveries and the rising costs of product development make public-private partnerships crucial. Future problems will require this critical mass of attention and broad range of expertise. To meet this challenge, the federal government can:

- Incentivize public-private partnerships focused on technology commercialization by initially targeting three to five high-priority problems for federal funding.
- Create councils of science and business leaders to address current industry challenges.

[3] *NCResearchCampus.net*

[4] *ncbiotech.org/COI*

Grand Challenge

Tackle the Issue of Abandoned Drugs and Critical Drug Shortages

From 2005 to 2010, we saw drug shortages triple. Currently, 178 drugs are difficult or impossible to obtain. Factors that contribute to this situation include issues in the supply chain, problems at the manufacturing plant, lack of production capacity, an increase in demand and lower profitability for manufacturers. Of the drugs in short supply, four out of five are delivered by sterile injection, which means that they require specialized manufacturing processes.

The keystone of this grand challenge solution is to remedy critical drug shortages while eliminating the limits that costs and profit place on drug production. We suggest a national Critical Drug Manufacturing Initiative, which would:

- **Provide a reliable production schedule for the manufacture of drugs that are in short supply.**
- **Establish a centralized Manufacturing Training Center for pharmaceutical manufacturing workers.**
- **Create a public-private forum to develop and improve best practices.**

To fund this new initiative, we propose a federal subsidy equivalent to $1 in new money to manufacture abandoned drugs or drugs in critically short supply for every $100 spent on researching new treatments and cures. This $1-for-$100 approach would alleviate the worst of the drug shortages. This funding would be deployed:

- **To existing drug producers, including contract manufacturers, or**
- **To a Critical Drug Manufacturing Center, a physical location with state-of-the-art facilities, subject-matter expertise in production methods, and world-class training in manufacturing. A non-profit CDMC could produce drugs at a modest premium above cost that would provide a shared revenue stream for the industry partner and the CDMC.**

As an example of the impact, using the current NIH budget of $34 billion, a $1 for $100 match would generate $340 million toward the production of abandoned or short-supplied drugs

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North Carolina Biotechnology Center

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11-117 CA 12/2011

North Carolina Board of Science & Technology

DEPARTMENT OF COMMERCE, STATE OF NORTH CAROLINA

December 5, 2011

Ted Wackler
Deputy Chief of Staff
Office of Science and Technology Policy
Executive Office of the President
725 17th Street, Room 5228
Washington, DC 20502

Dear Mr. Wackler,

On behalf of the Board of Science & Technology, a state-level Board administered by the North Carolina Department of Commerce, I am pleased to endorse the NC Biotechnology Center's Response to the following Request for Information (RFI): *Building A 21st Century Bioeconomy*.

Created in 1963, and composed of industry, academic, and nonprofit leaders from throughout the state, the Board is statutorily charged with identifying, supporting, and fostering research and development needs of both public and private institutions and organizations in North Carolina that relate to the state's economic growth and development. The Board has been responsible for numerous internationally recognized initiatives to catalyze the transformation of North Carolina's economy by leveraging research, science, entrepreneurship, and innovation. Examples include recommending organizations such as the NC Biotechnology Center (NCBC), the NC School of Science and Mathematics (NCSSM), and the Microelectronics Center of NC (MCNC), and leading strategic planning efforts such *Vision 2030*, *A Roadmap for Nanotechnology in North Carolina's 21st Century Economy,* and *Advancing Innovation in North Carolina*.

Several members of the Board of Science & Technology provided input to the Biotechnology Center's response, which addresses each of the RFI's major subject areas. It does so in two ways: first by describing each subject area and then articulating what North Carolina has done to address challenges in that area, and second by identifying a future challenge and proposing one to three actions the federal government can undertake to meet it. This approach draws on the nearly 30-year experience of the Biotechnology Center in supporting biotechnology research and development, business, education, and strategic policy.

We appreciate to opportunity to provide input on this important initiative, we hope you find the responses useful, and we welcome further dialogue on this topic.

Sincerely,

A. Blanton Godfrey
Dean, North Carolina State University College of Textiles
Chair, North Carolina Board of Science & Technology

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Creating Success
NC Community Colleges
Hope • Opportunity • Jobs

Growing the Life Science and Biotechnology Workforce in North Carolina
Connection, Entry, Progress, and Completion

Introduction

The over-arching challenge for the life science industry in North Carolina is to recruit, train, graduate, and place more students into the critical jobs that will help companies compete in the global marketplace. Over the last decade, North Carolina has felt the effects of the new world economy. In 1999, North Carolina had the 12th lowest unemployment rate in the nation. Today, the Department of Labor shows North Carolina declining to the 44th lowest rate. This is due in large part to the recession of 2008 and the migration of traditional manufacturing (textiles, furniture) in North Carolina to developing countries. Nearly every industry sector in North Carolina has been impacted negatively by the recession except for the biotechnology sector. This sector in North Carolina posted minimal growth between 2008 and 2010 but did not decline like other sectors. To continue to strengthen the sector it is imperative that the pipeline of workers for the life science industry be more highly trained than their counterparts in other countries in order to ensure that the companies in North Carolina maintain and grow their competitive edge in the global economy.

In response to this challenge, the NC Community College System recommends an approach based upon our experience with the since 2004 BioNetwork Initiative. This approach includes using a newly developed world-class talent management and economic development web 2.0 solution coupled with the on-going activities of BioNetwork's seven centers, NC Community College's SuccessNC initiative, and the outreach capabilities of the System's *STEM Bus*.

Background and Significance to North Carolina

In the early part of the 21st century, North Carolina took the mantle of biotechnology and, with targeted investments in workforce development, university research, education and facilities, North Carolina attained the number 3 spot in the country in that growing field. But how do we ensure that North Carolina doesn't fall behind in the coming years? One way is to make use of the foundation put in place through our biotechnology investment at our state's leading workforce training network, the NC Community Colleges, to expand its reach, streamline its resources and develop the education programs that will train the post-recession workers in North Carolina.

The recommended approach will help connect lower socio-economic, minorities, at-risk students, and the general populations to the education opportunities and careers available to them in the life science sector in North Carolina. The process follows a framework that has been the guiding foundation for NC Community College's SuccessNC initiative. This framework focuses on: a) how students obtain information and *connect* to education and careers, b) how they gain *entry* into training and education programs, c) how they *progress* towards attainment of credentials and degrees, d) how they *complete* programs of study and are placed into careers.

Description of Key Components

Connect:

- This process begins in K-12 where students are introduced to critical careers and plugged into one of the *online interactive* portals using the *STEM Bus*. These students and any student enrolling into a community college course will gain access to virtual career explorations and highly interactive and engaging 3-D immersive learning systems (www.launchingbrightfutures.com). Industry and businesses will be able to promote their companies by partnering and become a 3-D immersive world for students to explore and learn about the life science industry.
- An essential part of the recruitment of students will be appeal of the video game-like technology available on www.launchingbrightfutures.com and access via internet connections at public schools and community centers State-wide.

Entry:

- North Carolina will implement in January 2012 structured dual enrollment opportunities for high school students. Qualified juniors and seniors may enroll in college transfer and career technical education certificate programs in life science and engineering tracks. Qualified ninth grade students may enroll in Cooperative Innovative High School Programs that provide the opportunity to complete a high school diploma and an associate's degree in five years.
- Opportunities also exist for incumbent workers and career changers who complete BioWork to obtain credit in biotechnology associate degree programs at NC Community Colleges. Additionally, workers who have completed various third party industry-recognized credentials will be able to earn credit in appropriate associate degree programs.

Progress:

- BioNetwork's seven centers focus on creating and enhancing the training and education programs delivered through the 58 NC Community Colleges. BioNetwork was created through a grant from the Golden LEAF Foundation in 2004 and has grown and matured to account for over 200 new courses and course enhancements, over 10,000 trainees and students, over 50 life science customized training projects, and over 20,000 outreach/visitors to BioNetwork STEM bus. BioNetwork's centers and staff of subject matter experts is a vital part of supporting and growing the life science cluster in North Carolina.
- Mobile training provides increased flexibility to companies and students by taking portable high tech equipment and expert instructors on the road. Through BioNetwork, a mobile training trailer can be transported to an industry site. The trailer expands to accommodate 12 to 14 students and a wide variety of industry specific equipment.
- BioNetwork's BioEducation Center is a leader in developing advanced learning technologies for the life science and biotechnology programs at NC Community Colleges. These in-

clude simulation and gaming, multimedia learning tools, flash-based web tools, and virtual learning objects. Advanced learning tools are designed to enhance classroom learning and assist an instructor so that more time can be spent on hands-on training.

- A statewide comprehensive agreement between the NC Community College System, the University of North Carolina and selected NC Independent Colleges and Universities, the CAA ensures seamless transfer of up to 64 semester hours of credit and fulfillment of the undergraduate general education core for students who complete the 44-hour core or the associate's degree.

Complete:

- Through a partnership with the National Association of Manufacturers and Futures, Inc., a web-based portal (www.usmanufacturingpipeline.com) will be available to community college students through which they will be able to connect directly with employers, share online portfolios, learn about careers and companies, and identify opportunities for further education. Unlike job boards and other online career sites, this portal provides more functionality and security for students as they prepare their education and work portfolios.
- The NC Community College System and National Center for Biotechnology Workforce at Forsyth Technical Community College have also partnered with the National Association of Manufactures (NAM) to identify or create appropriate biotechnology industry certifications. Following NAM's Endorsed Skill Certification System for advanced manufacturing, the certifications will stackable with other lower level and higher certifications such as the National Career Readiness Certification or the North Carolina Processing Technician Certification.

ADVISORY COMMITTEE FOR

Biotechnology in the Piedmont Triad

A PARTNERSHIP OF PIEDMONT TRIAD CITIZENS AND THE NORTH CAROLINA BIOTECHNOLOGY CENTER

To the U.S. Office of Science and Technology Policy,

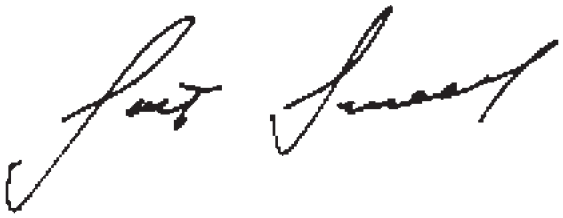
The Piedmont Triad region of North Carolina for a long time was known for tobacco, textiles and furniture. RJ Reynolds, Lorillard, Burlington Industries and others employed a large portion of our residents. We saw our economy change, and we lost good-paying jobs as the knowledge-based economy grew.

Over the last decade, this 12-county region that includes Greensboro, Winston-Salem and High Point has pulled together to develop the research and business infrastructure to support a high-tech economy. It began with the Winston-Salem Chamber of commerce and their blueprint to move toward a biotech and life-science economy.

Since then, we've developed two research parks, a joint school specializing in nanoscience and a wet-lab facility designed to serve as a launch pad for small companies. We've helped major companies like Targacept and Cook Medical grow. Our community colleges, particularly Forsyth Tech and Guilford Tech, have developed workforce training programs recognized internationally. And at the Wake Forest Institute for Regenerative Medicine, researchers are revolutionizing the way we think about organ transplantation.

Based on our experience and vision for the future, the Advisory Committee for Biotechnology in the Piedmont Triad has assembled a list of ideas. They include direct responses to the questions posed in the Bioeconomy Challenge as well as some ideas for the National Bioeconomy Blueprint. We also support the response of the North Carolina Biotechnology Center, included.

On behalf of the committee, we thank you for your attention,



Russ Read, Chair
Advisory Committee for Biotechnology in the Piedmont Triad and
Executive Director
National Center for the Biotechnology Work Force
Forsyth Technical Community College

Scott Sewell, Vice Chair
Advisory Committee for Biotechnology in the Piedmont Triad and
Vice President, Technology Acquisition & Development, Cook Medical

The Piedmont Triad is pleased to provide this information in response to the BioEconomy Challenge request for information. The input is based on North Carolina's success with building a life-science cluster.

The items listed below are not in order of importance and have been formatted as bullet points.

- Establish an FDA committee of academic and corporate leaders, including those from medical device, diagnostics and theranostics companies, to collaborate on the development and refining of predictive modeling programs for drug safety and efficacy. This could help reduce untoward side effects, costs and time from discovery to the marketplace.
- The FDA should:
  - (a) review list of FDA-approved indications for which INDs, clinical trials, and NDAs can be filed/conducted,
  - (b) review FDA-approved primary and secondary endpoint/outcome metrics. Researchers at prominent academic institutions are developing methodologies for measuring clinical trial results, but the FDA may not be coordinating with them.
- Establish an FDA subcommittee involving FDA clinicians/statisticians, academic researchers and life-science company chief medical officers to address unmet medical needs.
- To spur workforce development and economic growth, the federal government should establish a grant program to enable academic institutions to fund scientific/engineering internships at life science companies. This will broaden opportunities and stimulate interest in STEM education and provide win-win outcomes for students and life-science companies. The North Carolina Biotechnology Center's undergraduate and industrial (postdoctoral) fellowship programs are examples of successful models.
- With the assumption that life sciences companies prefer to hire locally, an obvious source for talent (i.e. laboratory technicians) is the community college system. The Associate of Applied Science degree programs at community colleges can be taken to the next level, particularly in nationally certified/credentialed programs, through federal reimbursement of tuition and related expenses directly to community colleges (subject to certain restrictions) for displaced workers receiving unemployment compensation who are seeking career changes into life sciences. This would help create jobs and provide a workforce-ready pool of talent.
- Encourage commercialization of new technologies through loan programs in the $100,000 to $250,000 range that don't require personal collateral such as the family home of an academic scientist or entrepreneur in loan guarantees, and simplify application forms.
- Advance the NIH initiative to establish a national translational research center/institute that can spur commercialization of basic university research discoveries via grants and other funding.
- Repeal that portion of the Patient Protection and Affordable Care Act which will institute a 2.3 percent federal tax on medical device company revenues in 2013.
- Support certification programs in development: Certification of specialized skill-sets affirms a knowledge and experience base for practitioners in a particular field, their employers, and the public at large. Working with partners at the national and state level, we aim to advance a process of adapting existing, or if necessary, creating the required certification for the biosciences technical workforce. (National Center for the Biotechnology Workforce, a NC BioNetwork Center, and the National Association of Manufacturers)

ARBORGEN®

Nancy M. Hood
Director of Public Affairs & Sustainability
Office:
Cell: [redacted]

6 December 2011

Mr. Ted Wackler, Deputy Chief of Staff
Office of Science and Technology Policy
Executive Office of the President
725 17th Street Room 5228
Washington, DC 20502

Via e-mail: bioeconomy@ostp.gov

Ref: Request for Information: Building a 21st Century Bioeconomy

Dear Deputy Chief Wackler:

On behalf of ArborGen Inc. and its employees around the globe, we would like to commend President Obama and the Office of Science and Technology Policy for taking this extraordinary initiative to build a 21st Century National Bioeconomy. This process of bringing together the thoughts and concerns of citizens and companies in the United States, who can support critical technologies through their research, development and commercialization skills, is an important first step in successfully reaching the Administration's goal of reducing our nation's dependence on non-renewable fossil fuels.

As part of our response, we will provide observations on the current regulatory process and offer some suggestions that could both make an immediate impact spurring the U.S. bioeconomy in the short-term while exploring issues that will require some long-term planning and adjustments. In this document, we will explore the following issues and topics in-depth:

- The importance of trees and biotechnology in emerging landscape of today and their potential transformative impact on advancing our nation's bioeconomy for the 21st Century;
- The difficulty and challenges of the current permitting process, which creates and insurmountable economic barrier for companies, from startups to even well-funded ventures;
- Recommendations on making permitting process more efficient, such as the increased usage of existing data to build more certainty and predictability in the NEPA process;
- The establishment of a "learn-as-you-grow-track" for non-food crops such as trees to provide economic relief and certainty during the permitting process.

By addressing these issues, we believe that the U.S. would be able to create a model that is economically viable and will unlock the economic and environmental benefits of biotechnology trees while maintaining a robust and comprehensive permitting process that will protect and preserve our natural resources.

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ArborGen's Role in a 21st Century Bioeconomy

ArborGen is a foundational company for a bioenergy economy, providing the roots and stems of an industrial raw material that is clean, environmentally beneficial, renewable and highly sustainable: commercial trees. Robust tree seedlings, bred with the best possible genetics, impact a National Bioeconomy at almost every level. Trees are a source of raw material for construction, furniture and paper, as well as for pharmaceuticals, both active and inert ingredients, and an endless array of cellulose-based materials. Trees provide a source of energy, sequester carbon and purify water. Trees are fundamental building blocks for community economies, jobs and industry. Purpose grown trees help manage precious resources, provide ecosystem services proportional to longer-lived plantations, help meet much needed conservation goals, and provide renewable raw materials for industrial use.

ArborGen agrees that 21st century advances in biological research and technologies are poised to return tremendous public benefits. At ArborGen we are perfecting methods through advanced breeding and biotechnology for improving wood quality; unlocking the raw cellulose in wood for improved manufacturing purposes such as energy and paper, and shortening time to maturity of high industrial value trees species such as Eucalyptus to ensure a sustainable supply under high and increasing demand; and helping responsibly integrate such species into the U.S. landscape.

ArborGen's technology platform represents more than 50 years of collective research and development and more than $200 million in capital expenditures, a level of dedication unrivalled in the forestry sector world-wide. With a focus on improving productivity and shortening growth cycles through conventional tree breeding and biotechnology, ArborGen has been focused on meeting an increasing global demand for traditional wood and paper products as well as providing sustainable feedstock solutions for renewable energy for more than a decade.

The world's population is now at seven billion people and expected to reach nine billion by 2050. As such, the global land base will remain our most critical and precious non-renewable resource. Maximizing the productivity of every acre designated for growing trees for human needs including food, wood, fiber and energy, and ensuring that each purpose-grown tree is planted for its ideal end-use will require new methods of cultivation, breeding, harvest and processing, as well as an advanced public acceptance of purpose-grown trees.

ArborGen is finding ways to unlock the potential of the tree by identifying and improving traits that meet important commercial needs. The lumber and pulp and paper industries, for example, have invested millions of dollars over the last century to breed trees for their ability to produce high value lumber first, and second to feed into mills for the extraction of fibers to make paper products. These programs have focused on developing a tree that most effectively meets the needs for wood and fiber. Loblolly pine is the prime example of a tree that has been significantly improved for a purpose by a responsible industry working to perfect a raw material to help keep pace with human consumption rates. Additionally, the tree is a storage container for carbon, even when the lumber is milled, the paper is rolled and furniture is crafted. When burned for energy, the carbon release is equivalent to that of the carbon stored, making the process carbon neutral. And trees are renewable. There is no plant species of greater value than the tree.

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Why Trees Are the Foundation for a 21st Century Bioeconomy

The challenge for ArborGen, as well as for a bioeconomy that offers biomass-based energy, is that the crops best suited to cellulose production for biomass – short rotation woody species such as Eucalyptus– bring new challenges to regulators. Though ArborGen believes that plants should all be reviewed equally and not singled out for scrutiny because one species is different from another, it is inevitable that perennials and long-lived species like trees must factor in the complexity of time. It simply takes longer for some species to reach maturity, which in turn creates longer timelines for deregulation and significantly higher proportional costs than is true of annuals such as corn and soybeans.

With the emergence of genomics, gene mapping, and genetic engineering, scientists are able to learn more about the mechanics of tree breeding than ever before and are rapidly striving to domesticate species for commercial purposes. Advanced breeding technologies such as cloning allow for standardization, which improves harvest and production efficiencies. Controlled pollination and hand selection have improved germplasm, improving disease resistance, straightness and branching of trees and improving per acre productivity. Technologies such as genetic engineering are now being applied to advance the performance of the tree for specific purposes, such as bioenergy, biofuels, pelleting and charcoal, as well as for improved growth, processability and stress tolerance.

In the United States, industrial production is limited by accessible hardwood trees, which provide needed high quality cellulose, a high-demand industrial raw material. They also have a higher BTU value than softwood making them preferred for energy production. Because hardwoods grow at a ponderous rate, are notoriously difficult to cultivate and are highly adapted to specific geographic locations, soil types and climates, the United States forestry industry has been only marginally successful at cultivating hardwood species in purpose-grown stands. Therefore, the greatest share of hardwoods for industrial use are harvested from forests managed to regenerate naturally, adding sustainability to the process, but not much toward supply predictability or harvest efficiency.

While hardwood species of high industrial value, such as cottonwood and aspen, are native to the United States, no native species has proven to be a solution equal to the value of an Australian native species, the Eucalyptus. Like the soybean (native to central China), this plant has a proven value well beyond its native habitat, and domestication for commercial purposes has proven to be of immense social, economic and environmental value. In the tropical and sub-tropical climate of Brazil for example, producers have adapted to growing non-native Eucalyptus species on what was formerly agricultural land. Cultivation of these trees has changed the economy of that country, creating a global leader in hardwood pellet, charcoal and cellulose production and export. At the same time, the purpose-grown Eucalyptus stands in Brazil are helping relieve pressure to harvest material for wood, fiber and energy from precious hectares of rain forest in this South American nation.

The value of the Eucalyptus species is so widely recognized that it became one of the first trees species to be mapped and sequenced through genomics. In an article published in *Biology & Nature* on May 12, 2011, Professor Zander Myburg[1] from the Department of Genetics and the Forestry and Agricultural Biotechnology Institute (FABI) at the University of Pretoria (UP) – in collaboration with the United States Department of Energy (DOE) Joint Genome Institute (JGI) – wrote that the genome

[1] http://esciencenews.com/articles/2011/05/12/eucalyptus.tree.genome.deciphered

sequence of the forest tree species, *Eucalyptus grandis* had been completed. In this article, Professor Myburg explains why this genomic sequencing project is of significant value to society:

> *Research is done on plants rich in cellulose (the main chemical component of wood), because glucose - the building block of cellulose - can be used in the production of biofuels and other renewable products. Eucalyptus trees grow very fast and can deliver the necessary biomass for making these bioproducts. Trees are advantageous when it comes to producing biomass. Unlike seasonal crops, they can be harvested year-round to supply a stable supply of biomass. In general they also don't compete with food crops. In addition, wood processing is well established in the pulp and paper industry. Similar processing can be used to isolate the cellulose from the wood for biofuels and other products.*

Because of their intolerance to cold temperatures, however, a very few varieties of commercially valuable Eucalyptus have been restricted to production in the southern most reaches of Florida and Texas. Because of the limited geography in which they can be cultivated, Eucalyptus has not been a viable alternative for providing a sustainable, reliable hardwood supply for U.S. industrial purposes.

ArborGen has a proven technology that can improve the cold tolerance of Eucalyptus, making it a viable species for purpose-grown hardwood stands in the Southern United States. In addition, ArborGen has been successful at modifying lignin ratios, a key technology to help unlock the valued cellulose trapped inside the structure of the tree. The U.S. National Renewable Energy Laboratory using an ArborGen modified Eucalyptus, has found that this tree releases more than twice the usual amount of sugar, making it a promising option as a biomass feedstock for liquid fuel[2].

Time and Scale Create Unique Barriers to the Deregulation of Modified Perennial and Long-Lived Organisms

ArborGen has been working toward commercialization of a hardwood Eucalyptus species engineered to improve its ability to tolerate freezing so that it can be grown in the Southern United States. Throughout the process of working through permits, gathering data, conducting studies and moving toward deregulation, ArborGen has experienced that when a species or technology is truly innovative and unfamiliar to USDA APHIS' Biotechnology Regulatory Services, it becomes subjected to significant delays in processing, and ongoing requests for additional data.

USDA is rich in institutional knowledge about row crops, with an entire branch of the organization dedicated to agricultural research – USDA's Agricultural Research Service (ARS). Within USDA, expertise also exists on the management of forests, but for public forest lands, not commercial forest lands. The government's institutional knowledge of specific species of trees, of diseases and pests of trees all exist in the United States Forest Service, but the knowledge related to growing, harvesting and managing commercial scale trees is tangential. The Forest Service's charge is to manage public lands, not to manage a commercial tree farm. Therefore, it is not surprising that when asked to deregulate a tree species modified for its commercial non-food value –ArborGen Freeze Tolerant Eucalyptus – USDA has been unable to call upon the same levels of institutional knowledge to get answers to questions in the same way it could for soybeans, corn or cotton. As a result, ArborGen's permits for field testing of

[2] Anglea Ziebell in a presentation to the 33rd Symposium on Biofuels and Chemicals held in Seattle, Wash., May, 2011.

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Freeze Tolerant Eucalyptus were in review at USDA's Biotechnology Regulatory Service (BRS) longer than any other plant species – 852 days. ArborGen's current permit for additional traits in Eucalyptus is the longest of all permits pending and currently in review at 282 days as of 11/30/2011 (the next longest being just 78 days).

The fact is that *7 Code of Federal Regulations Part 340* is a complex authority, so institutional knowledge and expertise offers an advantage to a familiar modified organism working its way through the regulatory system. It makes sense that for crops such as corn, soybean and cotton, institutional knowledge has helped the regulatory authority focus on the "plant pest risk" of the engineered trait, rather than spending valued time trying to accumulate useful knowledge about non-modified species. However, Freeze Tolerant Eucalyptus has proven that when that institutional knowledge does not exist, the permits and applications for the product are placed into a category that requires greater scrutiny and significantly longer timelines. Scrutiny is not, and should not, be a concern to any developer but the lack of predictability, evolving data requirements and the scrutiny itself is driving up costs and lengthening timelines, which is creating a significant barrier to success for ArborGen and for scientists who follow.

Lack of institutional data creates a system that invites other agencies to intervene with concerns that color and hamper action by the Biotechnology Regulatory Service. In our experience with Freeze Tolerant Eucalyptus, the Department of Interior intervened, concerned about its lack of institutional knowledge on the species, and attempting to bring its influence to bear earlier in the process of deregulation than has been seen before, at the permit stage. DOI's concerns are about the non-regulated species in general not distinct to the regulated tree. Fortunately, after many months of delays and discussions, DOI conceded that ArborGen's Freeze Tolerant Eucalyptus was not yet at the full commercial stage, but made it equally clear that this species would have to be held to a higher standard than any species previously deregulated.

DOI's desires for more information about Eucalyptus in the United States are valid. It is wise to learn more about this tree because it has been proven to be of such significant value as an industrial raw material. But rather than operating as if there is no knowledge about the species, the government should consider data that already exists in abundance in other countries where this same non-native species is being grown with tremendous success. Global data would firmly prove that where there are potential for negative effects of planting Eucalyptus, this species is easily managed and contained. The problem appears to be that the U.S. would prefer to rely exclusively on U.S.-based data and at large scale. Given the regulatory restrictions imposed prior to deregulation, gathering long term volumes of data for a long-lived species becomes economically prohibitive for small to mid-sized companies.

Equally complex is that in more than two decades of knowledge gained about genetic engineering and the astonishing safety record of biotechnology, the government appears to be less inclined to learn from its own institutional knowledge in this regard. According to testimony[3] from Jim Greenwood, chief executive officer of the Biotechnology Industry Organization, BRS now has substantial evidence to support the safety and efficacy of biotechnology in food crops:

[3] Testimony of the Biotechnology Industry Organization to the Subcommittee on Rural Development, Research, Biotechnology, and Foreign Agriculture, Committee on Agriculture, U.S. House of Representatives, June 23, 2011

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"Since the first crop developed through modern biotechnology was commercialized more than 15 years ago, U.S. producers have embraced the technology and grown increasing acres of biotech products. According to 2010 figures from USDA's Economic Research Service, 93 percent of soybean and cotton and 86 percent of corn grown in the U.S. were biotech varieties. Producers outside of the U.S. have also successfully utilized biotechnology: in 2010 more than 15 million farmers in 29 countries grew 365 million acres of biotech crops and trees. Nearly 50 percent of these crops and trees were grown by small producers in developing countries where rates of biotech adoption have been steeper than in industrialized nations. The expanding use of agricultural biotechnology throughout the world has made biotechnology the most rapidly adopted agricultural innovation in history"

To be clear, oversight of genetically engineered organisms falls squarely and solely under the Coordinated Framework and the agencies (USDA, EPA and FDA) where expertise in these organisms resides. Other agencies such as the Department of Interior, Department of Energy and the military, may have an interest in what is going on at BRS as biomass crops are being developed, but it is absolutely clear where the regulatory authority is and should reside.

We fully expect to see this exact scenario, intercession on behalf of other agencies, reluctance to utilize global data or call upon non-government expertise, repeated with any perennial species, any species being developed for biomass, and any species that is long-lived. Excessive costs created by delays when agencies have to negotiate with another, rising costs of research to provide additional data, and the built in calculation of the cost of NEPA lawsuits make the current roadmap for deregulation untenable for biomass crops.

Plant Pest Risk Analysis and National Environmental Protection Act

It is not the need for additional meaningful data, nor any lack of respect for the depth of understanding the government seeks that is a concern for ArborGen, it is the seemingly endless and unpredictability of the Plant Pest Risk Analysis, combined with the litigious environment created by application of the National Environmental Policy Act that becomes a barrier to entry for small business.

While ArborGen strongly supports the need for environmental responsibility and controls, the company is significantly burdened by the financial demands of litigation and a leaden regulatory system. Business succeeds on its ability to accurately predict economic outcomes both in the near and long terms. Under the current regulatory framework, our concern is that ArborGen's Freeze Tolerant Eucalyptus will continue to be held up in the system with no end in sight.

Significant delays in deregulation of Freeze Tolerant Eucalyptus have created timidity among investors who would otherwise see ArborGen as a great place to grow their capital. It is impossible for business investors to accept that once a proven technology goes into the regulatory system, their investment goes into a "black hole," with no predictable end in sight and no way to influence the outcome. Such behavior is not acceptable in business, but it is the status quo for our regulatory systems.

Biotechnology Regulatory Services appears to be overwhelmed by multiple aspects of the deregulation of Freeze Tolerant Eucalyptus:

1. Eucalyptus is not native to the United State. Even though non-modified species have been grown in the United States for many decades on thousands of acres with significant success as a mulch crop, the tropical and semi-tropical nature of the tree has limited its growth for successful commercial purposes to the southernmost reaches of Florida. Still, BRS seeks additional data on a broader scale to prove that Freeze Tolerant Eucalyptus is non-invasive.

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2. BRS lacks institutional expertise on commercial hardwood tree species: ArborGen's Freeze Tolerant Eucalyptus is the first commercial hardwood tree to be submitted for deregulation. In addition, institutional knowledge at USDA on commercial tree planting, harvest and marketing is nominal when compared to annual agricultural crops.
3. A reluctance to accept data from other countries where Eucalyptus has been successfully grown on millions of acres for decades. Eucalyptus is among the fastest growing hardwood trees in the world, is grown in more than 90 countries and represents eight percent of all planted forests. A large part of the global supply is concentrated in Brazil, with approximately 3.5 million hectares (a little over 8.5 million acres) in plantations. In 2003, global Eucalyptus pulp demand was eight million tons and it represented 40 percent of the world's hardwood pulp market.
4. Lack of clear guidance from BRS, most likely because of a lack of institutional knowledge or experience with such species, on evaluating perennial, long-lived plants such as trees and grasses.
5. A shift toward a precautionary approach that seeks to require "proving a negative." Whether in response to the European preference for the precautionary principle or excessive precaution promulgated by multiple NEPA lawsuits, BRS has become significantly more cautious in deregulating plants in the last decade, even with those species with which it has great familiarity.

In the case of Freeze Tolerant Eucalyptus, the agency is pushing for data that proves the species is non-invasive, or will not negatively impact hydrology. More than ample data is provided in the petition for deregulation to show that the hybrid used in is unlikely to be invasive, and in addition has effective pollen control technology, and has no native species with which to cross. In addition, a body of knowledge from growers on millions of acres in Brazil and other countries experienced with the hybrid has demonstrated that the species is non-invasive, and any concerns about hydrology can be readily managed. Still BRS is seeking precautionary levels of evidence. The only way to provide such evidence is through large-scale, long-term field trials. However, here in the U.S., especially with the conditions and limitations imposed as a "regulated article" under BRS' authority this would be economically impossible for a small company like ArborGen to support unless a commercialization option is made available, predictable and efficient.

Creating a Learn-As-You-Grow-Bioeconomy

A major source of the difficulty BRS is experiencing with Freeze Tolerant Eucalyptus is that it seemingly has only one track for all products to filter through its system. "One size fits all" does not apply easily to the abundance of variation in the plant and animal kingdom, so what has worked for soybeans does not work as well for trees. As a result the soybean, a crop that is planted in the spring and harvested in the fall, has multiple advantages over perennial trees that take years to mature: 1) BRS is familiar with soybeans (even though, like Eucalyptus, it is non-native to the US), 2) because soybean plants have been deregulated previously, 3) because USDA has institutional experience with soybean production, and 4) because the public is familiar with biotech soybean.

For trees, on the other hand, the data requirements and timelines are already extended simply due to a lack of practical knowledge and familiarity at BRS with the planting and harvest of trees. Time and scale

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becomes an almost insurmountable barrier to the regulatory process for trees. BRS "wants to know what it doesn't know, but doesn't know what it doesn't know". However, such exploration, while completely acceptable for scientific investigation, is lethal for a business endeavor. BRS is not charged by the government to engage in research, but to determine if existing research meets enough criteria to be deregulated. So when BRS seeks data to satisfy NEPA or the Plant Pest Risk Analysis on novel applications, the financial burden of long term, sustained research, under permit and evaluation, over multiple years before the process can move along is beyond daunting for investors.

Therefore ArborGen proposes a track that would allow a company to take a longer path to full deregulation, if and where absolutely necessary, working closely with BRS to "answer what it doesn't know" over time. The upside would be that companies taking this track would enter into a regulated commercialization agreement with growers at a scale that allows for meaningful data collection at a landscape level, and providing some return for the expense of research and development. The collection of data then becomes collaboration between government and a healthy industry, rather than an endurance test to see if a small company can financially survive the regulatory process.

Some of the criteria for a "learn-as-you-grow-track" already exist within the Part 340 Regulations, but have not been called upon as steps required for deregulation of the more familiar agricultural crops. As a result, concepts like partial deregulation and large scale permits have only rarely been used, so the agency doesn't have a "best practices" manual or even a simple "how to" guide to help staff administer these steps, which results in delays from yet another source.

Learn-as-you-grow would allow companies to enter into agreements with growers willing to take the extended risk and reap the expected rewards, while the government maintains oversight and continues to receive data from the developer. In other words, companies would be allowed to sell the plants to growers, work with growers and the government to extract important data, and then allow harvest of the trees at maturity to be sold for uses such as bioenergy, biofuels and paper products.

The result of such a system would allow a modest income stream to help offset the cost of production and research and development, it would allow for the long-term collection of important data without punitive action stopping the process, it would establish permission for large scale demonstration level plots to be planted and observed, and it would ensure that companies can continue to innovate and explore solutions to help meet demand for renewable energy and industrial raw material.

In practice, ArborGen and Biotechnology Regulatory Services are already exploring this second track for deregulation, although our discussions have not been identified as a second 'track'. However, it is patently clear that BRS wants additional long term data on this plant and that these data requirements exceed anything that has been previously required in a deregulation petition. It is equally clear that in at least two instances (invasiveness and absolute proof of pollen control) the agency is asking ArborGen to provide evidence of something that doesn't exist. Science cannot prove a negative, but over time, it is possible to rule out the negative on the weight of evidence that it has not occurred. ArborGen believes that in the case of Freeze Tolerant Eucalyptus, there is sufficient evidence to proceed with deregulation, but BRS is reacting from a lack of institutional knowledge and choosing instead to plunge headlong into the deep well of the precautionary approach in response to environmental groups who oppose biotechnology on an ideological level.

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ArborGen's Experience is Daunting to Innovators Who Would Follow

Research in forest biotechnology has become so difficult to conduct that leading academics in the field have stopped or limited their research in these important categories. Steven Strauss, PhD, of Oregon State University, along with prominent academicians Roger Sedjo, PhD, of Resources for the Future, and Mikaela Schmitt, PhD at the University of Indiana, sent up a distress call in the 2009 edition of *The Journal of Forestry*[4]:

> *Despite many dozens of research projects, hundreds of field trials, and a long-commercialized fruit tree, virus-resistant papaya, there continue to be very little public or private sector activity in the United States that is directed toward development of transgenic forest trees. We therefore undertook a survey of scientists knowledgeable in forest biotechnologies, breeding, ecology, and regulation to assess if they believed that the regulatory regime in the United States presents a significant obstacle to research or commercial development. Conducted in 2007, there were a total of 90 respondents (60% response rate) from throughout the United States. The large majority believed that regulations, in particular containment requirements during field evaluation, posed significant obstacles to development. Top priorities for research included development of gene containment methods and field studies of wood and abiotic stress modification. Priorities for regulatory reform included development of a tiered system and provisional authorizations to enable long-term field research.*

Currently research in tree biotechnology specifically aimed at the production of biomass for biofuels and bioenergy are limited to a small number of collaborations. ArborGen is involved in many of the funded joint projects, including the collaborations with the following institutions: Joint Bioenergy Institute (JBEI), Noble Foundation, University of Georgia, Clemson University, Mendel Biotechnology, Michigan Tech University, Oregon State University, North Carolina State University, University of Florida, and a USDA National Institutes of Food and Agriculture (NIFA) grant collaboration managed by the University of Tennessee. However, the research funded by NIFA is aimed primarily at production and harvest methods, not specifically at continuing or encouraging the vital research in tree biotechnology that can significantly impact a U.S. bioeconomy by ensuring a renewable biomass supply.

The time frame for environmental impact studies and environmental analysis alone requires an enormous commitment of time and money on behalf of the U.S. government as well as industry. The most troubling aspect of these studies for academics and companies (as should be for a budget conscious Federal government) is a highly unpredictable time frame that may allow the process to drag on for years. Perhaps the most immediate solution, other than amending or changing NEPA for clarity, would be for BRS to privatize the work of the studies themselves. Hiring private commercial or academic investigators to conduct these critical environmental studies may be a solution. Privatization will automatically make the completion of such reports a priority to the investigator, and perhaps some combination of public and private resources would ensure that the work gets done in a timely manner and without delays created by lack of funding, staffing or expertise with Biotechnology Regulatory Services.

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[4] Strauss, S; S. Sedjo and M. Schmitt, 2009, ""Forest Scientist Views of Regulatory Obstacles to Research and Development of Transgenic Forest Biotechnology," *The Journal of Forestry*, Vol. 107, pp 350-357

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Conclusion

ArborGen is supportive of environmental safeguards and ensuring that new technologies are safe to humans, animals and other plants. As an example of our commitment the company perfected a pollen control technology to help minimize any perceived impact to the environment just to ensure that every precaution was followed in developing Freeze Tolerant Eucalyptus. However, we believe that the body of knowledge developed over decades within the biotechnology industry should be ample evidence to make deregulation of new organisms relatively predictable and timely. The safety record of biotech crops is unmatched.

More applications are being submitted, more novel technology is being explored, and in spite of an enormously successful track record, the United States appears to be drawing ever closer to a precautionary approach, which requires proof of damage that has not occurred – proof that something does not exist, a scientific impossibility.

Because of this drift toward ideology and away from science, it is more difficult today to get even a familiar annual crop deregulated in a timely manner. The process is greatly magnified for crops with which Biotechnology Regulatory Services and the United States Department of Agriculture lack institutional knowledge or experience. For a highly versatile perennial crop that can provide a sustainable, renewable source for industrial raw material, such as Freeze Tolerant Eucalyptus, a different track must be developed to allow for commercialization. If our leadership is unable to learn-as-it-grows with crops that may take a decade to mature, then the burden of regulatory oversight and the cost of litigation will prohibit innovation in the United States and more technology will go off shore where it can thrive.

We sincerely appreciate your consideration of this submission, and we, at ArborGen, would welcome the opportunity to discuss our proposal in greater detail with you or the professional staff at OSTP should such opportunity present itself.

Respectfully submitted,

Nancy M Hood
On Behalf of ArborGen Inc.

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NATIONAL BIOECONOMY BLUEPRINT
Response to Request for Information: Building A 21st Century Bioeconomy

Prepared by Tufts University

Introduction

Biological research throughout the United States is a crucial aspect of the national economy, through the staff employed by laboratories in universities and other research institutions, through the operation of research facilities, as well as the application of the knowledge created. Currently, Tufts University employs approximately 600 faculty engaging in research and education that supports the bioeconomy, from basic scientists to clinical researchers and practitioners to those involved in the development of policy as research moves into the marketplace. Supporting our faculty are many more (over 3,000) laboratory assistants and technicians, administrators serving labs, departments, schools and the university, librarians, and those devoted to facilities maintenance, security, and infrastructure. Tufts also has currently more than 9,500 graduate and professional students enrolled, and more than 2,500 of these are in biomedical fields, with many others in fields that have applications to biomedical science. These students play a tremendous role at Tufts, both as the scientists of the future, and as one way in which new collaborations are formed, both informally and through formal educational initiatives.

As with many research intensive institutions throughout the US, Tufts University faces a range of challenges with regards to extramural funding and translating research to the marketplace. With budgets of Federal funding agencies continuing to be flat or even reduced, we will continue to face challenges of how to continue to conduct innovative and transformative research in the fields of basic and clinical biomedical research and policy. Tufts has an immensely diverse research portfolio, and is characterized by its priority for collaboration across the various Schools and Centers. We seek to support this research program, and to look for new and creative ways to ensure that our research program continues to grow and, ultimately, to support the bioeconomy of our region and beyond.

Team science in the biomedical sciences is a tremendous cultural shift for the discipline, particularly with regards to integration with such diverse fields as mathematics, physics, modeling, and computer sciences. One hurdle that such teams face is the physical organization of scientists. While technologies have increased the degree to which researchers can collaborate over distance, the formation of teams is facilitated primarily by physical proximity. Programs that both provide incentives for new interdisciplinary teams to form and that provide a space for scientists to formally and informally meet and discuss their research projects are essential to the development of cutting edge team science.

Over the past several years, Tufts has worked to address this challenge, and to strengthen the bioeconomy in our region through increasing and improving our research infrastructure. In 2009, Tufts Cummings School of Veterinary Medicine opened the New England Biocontainment Laboratory. Built with funds from NIH, this BSL-3 laboratory serves Tufts, other New England universities, and the private sector for the study of infectious diseases as well as for biodefense research. Also in 2009, Tufts University School of Dental Medicine opened its 5-story, 95,500 sq ft LEED-certified expansion on top of the existing School's building. This space supports additional training and research efforts, in addition to adding 73 new treatment centers, with the capacity to care for 20,000 patients a year, many of whom have no or limited dental insurance. In 2009, the School of Engineering opened the Proof of Principle Lab to support collaborations between the university and industry and promote translation in areas including tissue development, drug delivery, optics, and optoelectronic technologies.

With $1.6 million from the NSF, the Tufts Department of Civil and Environmental Engineering is creating a state-of-the-art Environmental Sustainability Lab that will support multidisciplinary experimental and mathematical modeling research on such issues as the effects of nanoparticles and pharmaceuticals in water, soil and other media. The Department of Biology in the School of Arts & Sciences has received funds from NIH to support the creation of new laboratories that will allow for more collaboration and integration of its basic and translational research programs. Tufts also has

plans to expand core facilities to support an increased need expressed from faculty and is working to renovate existing laboratory spaces throughout the Boston Health Sciences Campus.

These construction projects support a growing biological and biomedical research community at Tufts University. This growth is due to initiatives at the School and Central Administration level to support multidisciplinary and collaborative research projects. In 2005, the Office of Proposal Development was created to support groups of faculty to write and submit multidisciplinary proposals. In 2008, Tufts received an NIH Clinical and Translational Sciences Award for the creation of the Clinical and Translational Sciences Institute, which provides resources for faculty throughout the university to reduce the barriers for multidisciplinary research projects. Additionally, in 2010, the Provost instituted the Tufts Collaborates! seed grant program, to provide new groups of faculty with the funds necessary to develop preliminary data and solidify new interdisciplinary collaborations.

Research is not only part of the bioeconomy, but it is also the very foundation from which the bioeconomy must build its success, and any national blueprint must incorporate an aggressive and robust research portfolio to bolster efforts to expand the bioeconomy.

Grand Challenges

Question 1: Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, nonprofit organizations, foundations, and other stakeholders to achieve this goal.

In an increasingly globalized society, the bioeconomy is, by necessity, connected through many layers, from international trade and commercialization to regional efforts to local universities. These layers, however, are not well integrated at this point, and there are barriers at each level to developing and supporting research that has global impact. These include access to investment capital as well as fair and reasonable approaches to intellectual property rights. Chief among these barriers is the so-called "valley of death" – limited amounts of capital to support the development of early stage discoveries, curtailing or even obliterating the opportunity for innovative discoveries to reach the market place.

Addressing grand challenges requires a genuinely interdisciplinary approach and requires input from both individual researchers and large multidisciplinary centers. One barrier to such collaborations is the current mechanisms for funding. Federal research funding opportunity announcements increasingly state that programs seek interdisciplinary approaches to currently intractable scientific problems. However, mechanisms for funding such large programs (e.g., NIH's program project grants) are used infrequently by many Institutes and Centers. Furthermore, without mechanisms to support collaborations in advance of these larger awards, individual researchers see little benefit in forming interdisciplinary groups far enough in advance of potential funding opportunities to be competitive. Specific RFAs from NIH and USAID (in particular) and NSF (to a lesser degree) are released with little time for groups to form – researchers must already have in place substantial preliminary work and evidence of existing collaborations to be competitive – and the current system of releasing one-time RFAs for particular challenges does not encourage new and potentially highly innovative collaborations to form, but rather rewards existing collaborations.

Grand challenges should be identified through a fully interactive process involving Federal agencies, academia and industry, similar to NAE Grand Challenges for Engineering. Through a multilevel process involving multiple stakeholders, Grand Challenges can be targeted both to national need and to feasibility. This process can likewise encourage academic, industry, and community stakeholders to work together to eliminate barriers to bringing findings from these Grand Challenges to the marketplace in an efficient and effective manner. Ideally, this process should involve discussion, both through online technologies similar to discussion boards and wikis and through real-time webcasts or similar formats, in addition to more traditional Requests for Information. In this way, a genuine conversation can occur, and questions can be posed and answered more immediately.

A crucial need exists to coordinate and network existing research, involving universities, industry and non-profits, to maximize the impact of the research and to address the Grand Challenges. These 'bioeconomy consortia' must have minimal barriers to participation. One way to encourage these multi-institutional consortia is to adopt a Federal-wide approach to proposal submission similar to NSF's 'collaborative' proposals. Instead of requiring a lead institution and subcontracts for other participating institutions, NSF allows, for many funding opportunities, two institutions to supply independent yet linked budgets and other materials. Thus, each institution has the ability to request full indirect costs, the lead institution has reduced administrative burden, and each institution is seen as an equal partner in the research endeavor.

Research and Development

Question 2: Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the federal funding priorities in research technologies and infrastructure to provide the foundation for the bioeconomy?

Traditional life sciences and basic research must be included in the bioeconomy blueprint. While basic science research has popularly been known as "seeking knowledge for knowledge's sake," this research provides the foundation on which the bioeconomy rests. Basic research is frequently the venue through which therapeutic targets are uncovered, and the concept of personalized medicine indicates that we are still lacking an understanding of potential therapeutic targets. A number of Tufts scientists are currently supported by Federal funding to conduct basic science that has great promise for future marketable products. For instance, Abraham L. Sonenshein is investigating the mechanisms by which two related bacterial species control the flow of metabolites between central carbon and central nitrogen pathways, thus allowing a deeper understanding of pathogenic mechanisms and may aid in designing novel inhibitors of pathogenesis. Jonathan Garlick studies the potential for pluripotent human embryonic stem cells to bioengineer oral mucosa for regenerative medicine. Philip Haydon is investigating the role of astrocytes in regulating neuronal receptors that are essential for synaptic plasticity and learning and memory. These receptors are thought to be involved in several disorders, and his research may lead to the identification of novel therapeutic targets. David Kaplan researches at the interface between biology and materials science and engineering to understand and control biological synthesis and the processing of biopolymers. Studies focus on the manipulation of human cells on novel matrices in bioreactors to generate desired tissue outcomes for engineered tissue replacements and 3D disease models for therapeutic drug discovery.

Additionally, basic research in the bioeconomy includes such areas as computational epidemiology, biosensing, and green energy. Elena Naumova's multidisciplinary work in the fields of computational epidemiology, conservation medicine, and biostatistics improve the quality of basic biomedical research with analytical tools for researchers and policy makers. Fiorenzo Omenetto, with David Kaplan, has identified bio-friendly polymers to serve as platforms for optical and electronic components that seamlessly integrate with the environment and with living tissue. By exploiting these biopolymers to produce mechanically robust, biodegradable technological materials platforms, a new generation of flexible electronic and optical systems and devices for medical and environmental applications can be developed. Matt Panzer's research efforts are motivated by the challenge to capture, convert, and store solar energy with nanostructured thin film photovoltaics to develop novel solutions that meet global energy demands.

Complementary approaches are necessary to drive innovation and address the underlying questions on which the clinical needs rest. Both funding for single topic areas in basic research and for multidisciplinary (and multi-agency) translational science programs are necessary, particularly to pursue breakthroughs in personalized medicine. One approach from NIH has been to ask applicants to describe the relevance to human health of the proposed research. While this method of ensuring that NIH's mandate is met is necessary, it has resulted in the perception that basic research is less valued and less likely to be funded in a highly competitive environment. At the same time that the budgets of

Federal agencies are unstable, NIH has, under Dr. Francis Collins' direction, introduced an increased priority on immediately translational research. Many basic science researchers view this direction as a betrayal of the work they do. To ensure that basic biomedical research continues, other agencies may need to have increased funding specifically for this sort of research.

Furthermore, much basic research does have a more immediate connection to potentially marketable applications. For these researchers, multi-agency, multidisciplinary funding opportunities can have a tremendous impact. An example of this sort of program is the NSF/NIH Evolution and Ecology of Infectious Diseases solicitation. This program seeks multidisciplinary teams that can approach the question of infectious disease transmission dynamics in many ecosystems and for all life forms, including zoonotic and plant disease as well as links to human health. Through mechanisms such as these, basic scientists can partner with clinical researchers, epidemiologists, social scientists, clinicians, and others to gain a broader understanding of both the underlying mechanisms and the environmental factors for disease transmission, thus providing the broader scientific community and policy makers to be able to predict and respond to future outbreaks.

Despite constrained budgets, high-risk, high-reward research must be supported. NIH has a mechanism by which these projects can be funded: the Exploratory/Developmental Research Grant Award (R21). However, the R21 mechanism, through which researchers can request up to $275,000 for up to 2 years, is often seen by both researchers and reviewers alike as a "mini" research grant, and the expectation for substantial preliminary data (which are technically not required) prevents many researchers who wish to explore a new direction from applying for this mechanism. To ensure that these potential breakthrough ideas receive adequate funding, the review system for R21 proposals should be revised, through separate panels and an increased focus on the existing "innovation" review criteria. Additionally, the Small Grant (R03) program should be expanded to fill the role that the R21 is by default filling – to provide a way in which additional preliminary data can be developed in preparation for a larger research grant.

Research funding should support truly interdisciplinary projects where all disciplines drive the research. A high-impact initiative of Tufts University is the Jean Mayer USDA Human Nutrition Research Center on Aging. As the largest research center in the world investigating nutrition and its role in age-related chronic and infectious diseases, the HNRCA's research is supported by Agricultural Research Service (ARS), the intramural research arm of the USDA, as well as by other federal and, to a far lesser extent, non-federal grants. Twenty research laboratories, supported by 270 researchers, trainees and staff as well as nine Core Units, comprise the HNRCA. While all research conducted at the HNRCA is related to the overall themes of nutrition and aging, these labs employ diverse research methods, including cellular and molecular studies, animal studies, human metabolic studies and epidemiological research, thus increasing the HNRCA's capacity for truly transformative and translational research. The current Strategic Plan released this year notes seven scientific priorities for the next five years:

- Nutrition and Neuroscience
- Nutrition and Functional Genomics
- Obesity and Aging
- Nutrition and Chronic Diseases of Aging, with a focus on Cancer and Cardiovascular Disease
- Inflammation, Immunity, Infectious Disease and Aging
- Musculo-Skeletal Defects Leading to Decline in Function in the Elderly
- Micronutrients and Healthy Aging

Each of these areas necessitates a multidisciplinary and collaborative approach, and will require the creation of teams within the HNRCA and between the HNRCA and the other Tufts Schools, including Engineering and Medicine, and between the HNRCA and external partners, including industry and non-profit organizations. Because of the HNRCA's commitment to use its research findings to educate the public, healthcare providers, policy makers, industry and the scientific community in related fields, the impact this Center can have will continue to be felt nationally and globally.

Likewise, the School of Engineering receives federal and non-federal funding in support of cross-cutting strategic areas selected to provide opportunity for societal impact. This includes engineering for human health, sustainability, and the human/technology interface. A component of this – Water: Systems, Science, and Society (WSSS) – provides unlimited collaborations. The WSSS encompasses participants from five of Tufts graduate schools, tackling challenges from coastal flooding to the spread of infectious disease.

Question 3: What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

The critical technical challenges needed to advance high throughput approaches include data management, imaging, and design of new materials and technologies.

Through its Molecular Libraries Program and other research activities that will be part of the new National Center for Advancing Translational Sciences (NCATS), NIH is supporting several projects that use high throughput technologies in genetics and drug discovery. These activities will certainly help to accelerate translational research programs that could result in drug development. For instance, many researchers at Tufts work on the discovery of targets for drug discovery. Daniel Jay receives NIH support for his research on cancer and the mechanisms through which cancer is dispersed. This research allows the prediction of optimal drug regimens, complementing pharmacogenomics. But to advance Dr. Jay's research so that it will reach the clinic, Dr. Jay will need to collaborate with a biopharmaceutical company that can help him to optimize drug candidates. In collaborations such as this, one that will translate basic research into clinical compounds, it will be necessary for both parties to share reagents and collaborate openly, and to recognize the value of intellectual property that may be jointly owned.

A major challenge is to manage and interpret large volumes of data. Tufts University has a number of resources available to researchers to approach this challenge. The NIH-funded Tufts Center for Translational Sciences Institute (CTSI) supports both the Biomedical Informatics component, which provides the infrastructure for communication among CTSI researchers, and the Research Design Center, which assists researchers in study design, the creation of secure data collection systems, and data analysis. Additionally, Tufts University Information Technology recently launched a new research cluster that harnesses the power of many computers, called nodes. With the improved 64-bit cluster, a researcher can do more calculations in a shorter amount of time than by using only one computer. The NSF-funded VisWall, the centerpiece of Tufts' Center for Scientific Visualization, further provides researchers with ways of analyzing data. The state-of-the-art rear projection system allows researchers to create 3D models of data, and it has been used in such fields as fluid dynamics, geotechnical engineering, human factors in medical systems, image reconstruction and tomography, computational geometry, robotics, chemical mechanical planarization, computational anatomy and visualization itself.

Adding new technologies is essential to this part of the research enterprise, and computer systems for data analysis and management have advanced with tremendous speed. In response, Federal agencies should support the acquisition of such systems for academic institutions, individually or in consortia with other institutions and industry. Because the technological capabilities change rapidly, proposals for such systems should be reviewed and funds released as quickly as is practical. In this way, the research infrastructure throughout the United States can be substantially improved, allowing for greater ease of inter-institutional collaborations, data sharing, and data management.

Question 4: The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly known or unknown functions. All areas of scientific inquiry

that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein functions for genes?

To revolutionize the prediction of protein functions for genes requires the construction and analysis of models of large, nonlinear dynamic networks that span several spatial and temporal scales. Multidisciplinary, multi-agency funding efforts are needed to develop multi-scale modeling that can integrate genomics data with environmental, protein, and network data to elucidate connections and fully understand biological systems. One example of collaborative research funding in this area is the NSF Division of Mathematics Sciences (DMS) program with the NIH National Institute of General Medical Sciences. This program funds projects on the application of mathematics to biomedicine. Currently, Tufts has mathematicians working on such problems, including Christoph Börgers who is funded through the NIH/NSF Collaborative Research in Computational Neuroscience program and, with mathematics professor Scott MacLachlan, through the NSF.

In addition to technological advances, to increase the capacity to extract information from genomes requires human capital. Increasingly, this gap is apparent in many quantitative fields (see, for instance, the "crowd-sourcing" of data analysis in such diverse fields as the Search for Extraterrestrial Intelligence, the identification of whale songs, and even a multiplayer online game to solve problems in protein folding). For biomedical research, however, there is an increasing need for those trained to help biologists understand existing data. As discussed below (see Workforce Development), most Federal funds to support training are for the doctoral level and above. To fill this need for additional human capital, Federal agencies can support those pursuing master's degrees in fields crucial to understanding these existing data, in addition to continuing to support doctoral and postdoctoral training.

Moving Life Sciences Breakthroughs from Lab to Market

Question 5: What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

There are a number of barriers preventing research discoveries from moving from the lab to commercial markets. Often, university faculty may not be aware of the steps they will need to take to optimize their discoveries, particularly if they are working on new chemical entities or novel biologic therapies. An entrepreneurial ecosystem within the university can accelerate commercialization of basic research by providing investigators access to resources such as venture mentoring, angel investors, and business advisors, all with the goal of developing and maximizing the value of university intellectual property.

A second barrier is lack of proof of concept funding to help technologies and inventions bridge the "valley of death." Federal funds can help to bridge this important gap in translational research, in part through changes to SBIR and STTR programs, as described below.

Question 6: What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of Federally-funded bioeconomy-related research?

To help to address the "valley of death" for early stage discoveries, changes in the SBIR and STTR programs can provide greater support to researchers in the early stages of discovery. For instance, more flexibility in the SBIR program for proof of concept funding or pre-incorporation activities could allow these investigators to bring their research to a stage where they will be seen as a lower risk investment for venture capital firms or other private entities.

Likewise, STTR funds could be used for patent protection and proof of concept programs, replicating the success of organizations and approaches such as the Coulter Foundation. The Coulter Foundation provides funds to biomedical engineering departments, and oversight committees are formed at each university with representatives from the medical school, the Office of Technology Transfer, entrepreneurs, local Venture Capital, and the Business school. With these stakeholders' involvement, the advances in biomedical engineering have a greater likelihood of surviving the "valley of death."

Question 8: What are the challenges associated with existing private-sector models (e.g., venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

Currently, venture funding is de-risking investment, in part due to the US economic difficulties; as a result, limited venture capital funds are focused more on later stage technologies. Federal funding in the form of larger amounts of SBIR funding so that biopharmaceuticals can be sufficiently de-risked would help to address this. In this way, Federal funding can act as a catalyst to bring private money and risk capital to the table.

Additionally, new federal programs can be created within existing funding streams to leverage angel investors or venture funds. One possibility is to create a federal proof-of-concept center, or a core facility that can be accessed by SBIR-funded companies. These resources will help to bridge current gaps, while making start-ups more attractive to venture funds.

Workforce Development

Question 9: The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Training for scientists and engineers should explicitly foster skills needed for the bioeconomy workforce. These skills include the ability to work in diverse teams that straddle expertise areas and disciplines, innovative thinking oriented toward solving real-world problems, and communication with non-scientists. Most support for such training is at the doctoral level and above.

Currently, Tufts has approximately 12 NIH-funded institutional training grants, each of which offers the opportunity for predoctoral students to engage in cutting edge interdisciplinary research and training. For instance, as a researcher at the HNRCA and faculty member at the Friedman School of Nutrition Science and Policy, Dr. Andrew Greenberg's T32 focuses on nutrition as an underlying component of many chronic diseases and his training program gives the next generation of researchers the tools to address chronic disease prevention at the molecular, cellular, organismal and/or population levels. Similarly, Dr. Alice Lichtenstein, HNRCA research scientist and Friedman School faculty member, leads a predoctoral training program in nutrition and cardiovascular disease at the basic, clinical, epidemiological and/or translational level. Dr. James Schwob of the Tufts University School of Medicine leads an NIH-funded training program that is specifically designed for MD/PhD students and to bridge the communication and cultural divide that too often separates scientists and clinicians, thus providing students with the tools they need to successfully meld the two arenas.

To supplement these excellent training programs, support for those pursuing master's degrees should be available. Currently, there is an ongoing discussion about the future of the biomedical workforce, most notably illustrated by the recent NIH RFI on the topic. At Tufts and other institutions, there is a need for training at the master's level and below to train excellent scientists who can be a part of a support team for PhD-level scientists, as laboratory technicians, data miners, and experts in modeling, mathematics, and computer science. Many have noted a glut of PhD-level scientists, and the current training grants available, as well as the culture in many fields of awarding MS degrees to those who do not complete a PhD as a sort of "consolation prize," reinforces the idea that the PhD track is the only acceptable pathway to a career in biomedicine or related fields. Programs like the NIH T32 could be

adapted for MS programs, and programs such as NSF's IGERT could be expanded to include MS students as well as PhD students. For each of these, the priority for funds should be for those training programs that have a truly interdisciplinary focus.

Scientists and engineers in both academia and industry will need appropriate awareness of the interdisciplinary research questions central to the bioeconomy. It will be critical to train biological scientists with highly developed quantitative skills, as well as physical scientists and engineers with appropriate awareness of challenges in the life sciences. Federal programs should support university efforts to develop curricula and programs focused on horizontal integration of training across disciplines while maintaining appropriate in-depth training in students' core research areas. Tufts has a demonstrated commitment to STEM education throughout the pipeline. For instance, faculty in the Department of Biomedical Engineering involve high school, undergraduate, and graduate students in team research, and many of these are from underrepresented groups. Additionally, Henry Wortis, of the Sackler School for Graduate Biomedical Sciences, leads the NIH-funded Post-baccalaureate Research and Education Program (PREP), designed to provide a bridge from undergraduate to graduate studies by allowing five students a year to "apprentice" in a scientist's laboratory.

The NSF Integrative Graduate Education and Research Traineeship program is an example of a Federal graduate training program that encourages mentorship, career development, hands-on experience with innovation and translating research discoveries to solutions for societal challenges. These best practices should be expanded beyond the frontier interdisciplinary programs that IGERT supports to graduate training across the life and physical sciences and engineering. The NSF REU program accomplishes similar aims with undergraduates. The School of Engineering has received multiple awards to support student research projects during the summer, as well as support from the NIH (ARRA funding), opening students to the possibilities of research.

Programs that support network creation, workshops, travel and summer programs for researchers are useful to raise awareness across scientific communities about science at the interfaces among disciplines. Tufts University has developed a number of ad hoc programs to address this need, including annual Research Days, sponsored by the Office of the Vice Provost. These day-long seminars feature Tufts researchers presenting talks and poster sessions on a particular scientific theme with focus on the various approaches to research on that theme, from molecular biology to drug discovery to clinical trials to policy implications. Similarly, Tufts had its first Science Day, which focused specifically on interdisciplinary research, and featured talks on the barriers to such research, the successes achieved, and strategies for improvement. Both of these initiatives have resulted in new collaborations both within Tufts and between Tufts faculty and industry representatives who attended.

With a relatively modest Federal investment, such programs as these can be expanded beyond a single institution to regional or national conferences that encourage and facilitate a greater understanding of the research conducted and its broader applications and that foster increased collaboration. With "Sabbatical" cross-disciplinary opportunities for post-docs and graduate students, these programs can help to create a community of researchers alert to and equipped to conduct interdisciplinary research, thus resulting in a cultural shift away from disciplinary "silos." The new NSF Science, Engineering, and Education for Sustainability Fellows is an example of a program that supports this type of activity.

Fellowships that allow students to spend part of their graduate careers working in industry or other sectors help create networks between academia and industry, foster real-world learning, and provide students with greater understanding of workforce opportunities beyond the university lab. Collaborative research with industry and orienting research toward grand challenges defined in concert with industry help foster student awareness of industry challenges and skills. The NSF Grant Opportunities for Academic Liaison with Industry (GOALI) program is an example of Federal funding that catalyzes industry student exchanges and research collaborations.

Question 12: What role might government, industry, and academia play in encouraging successful entrepreneurships by faculty, graduate students, and postdocs?

Currently, academic researchers face many challenges when seeking opportunities for entrepreneurship, as discussed earlier. Federal funding in the form of supplements to research grants for commercialization opportunities and programs devoted to entrepreneurship and commercialization (such as NSF's I-Corps, Small Business Administration centers, Department of Commerce activities, and University Centers of Excellence) can help to overcome these barriers. Additionally, providing funds for partnerships with business schools will help to mentor students and postdocs in entrepreneurship and business plan building. These partnerships can further help to demystify the process of licensing technologies or explore business start-up opportunities, and help to create a culture in which these activities are encouraged at all levels of faculty and administration.

Furthermore, to minimize conflicts in intellectual property ownership and protracted negotiations on the value of early stage IP, Federal programs should focus on open innovation, as in models like Pfizer CTI.

Public-Private Partnerships

Question 16: What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

Essentially, the importance of university and non-profit research institution participation in successful public-private partnerships and actively growing innovation ecosystems must be recognized. These public-private partnerships should focus on the development of an active ecosystem, in which the private sector can provide the infrastructure, and the public sector should provide proof of concept funding for new start-ups. To maximize the leverage of Federal dollars, matching programs, in which private and/or state funding is required, can further strengthen these partnerships, and a shared goal of sustained partnerships should be shared by the institution and the public entity.

Question 17: What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for precompetitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

Barriers to precompetitive collaboration are often highly related to the potential for profits, and to the control of intellectual property. Industry is often hesitant to share technologies or expertise given the need for transparency and open source in many precompetitive efforts. Additionally, industry is highly motivated in speeding regulatory processes, especially with the FDA. Buy-in from the FDA in precompetitive, engineering-based approaches to either continuous manufacturing technologies or personalized medicine is a high-impact opportunity.

Another highly promising approach to pre-competitive collaboration in the life sciences is the integration of scientific disciplines, such as engineering and medicine, in initiatives such as the Koch Institute at MIT, which is focused on engineering and cancer. These multidisciplinary approaches to problems can yield novel therapies and devices, and funding for these types of initiatives should be increased. Furthermore, these initiatives should be developed in such a way as to facilitate innovative collaborations among different disciplines, as well as to include those with expertise in translating findings from the bench to the marketplace.

Dear Mr. Wackler,

On behalf of the Coalition Advancing Multipurpose Prevention Technologies (CAMI) and the Initiative for Multipurpose Prevention Technologies (IMPT) we are pleased to submit the attached Request for Information (RFI) entitled **'Building a 21st Century Bioeconomy: The Case for Multipurpose Prevention Technologies'**.

Below are URLs to two documents relevant to this RFI:

Advancing the Scientific and Product Development Agenda. Report of an "MPT Think Tank" (Executive Summary). Washington. DC, USA; May 2011. Hemmerling A., Harrison P., Young Holt B., Manning J., Stone A., Whaley K.
http://www.cami-health.org/documents/050511-MPT-ThinkTank-Executive-Summary.pdf

What Regulatory Guidance Exists for Multipurpose Prevention Technologies (MPTs)? A Review of Key Guidance Documents and Their Applicability to MPTs. Martha Brady and Heeyoung Park. Population Council, 2011
http://www.cami-health.org/documents/What%20Regulatory%20Guidance%20Exists%20for%20MPTs.%20Pop%20Council.pdf

Thank you for the opportunity to submit this RFI. Please contact us if you have any questions.

Sincerely,

Bethany Young Holt, PhD MPH
Executive Director, CAMI | IMPT
Public Health Institute

and

Kevin Whaley, PhD
Executive Advisory Member CAMI | IMPT

Building a 21st Century Bioeconomy: The Case for Multipurpose Prevention Technologies

Introduction:

Every day, more than 1,000 women die from preventable causes related to pregnancy and childbirth. Worldwide, some 75 million unintended pregnancies take place each year and almost half of all pregnancies in the United States are unintended. . Millions are also at high risk of sexually transmitted infections (STIs) and the serious diseases which are often associated with them and take a large economic and social toll on countries. As just one example, the financial burden of dealing with STIs in the United States amounts to about $15 billion annually in direct medical costs alone. Among those burdens is HIV, which remains a serious and challenging global health issue, with 33.3 million people now living with HIV and 2.5 million new cases occurring each year.

Despite the obvious biological, behavioral, and physiological linkages between the risk for unintended pregnancy and STIs, researchers working to prevent pregnancy, HIV, and other STIs have traditionally worked independently in "silos", tackling these interconnected challenges separately. The Initiative for Multipurpose Prevention Technologies (IMPT) has been formed to break open up these silos by providing a steady stream of information and convening researchers, product developers, advocates, and funders to prioritize development of **multipurpose prevention technologies (MPTs)** that can -- simultaneously -- address these reproductive health risks.

The IMPT is driven by the conviction that such lifesaving, potentially cost-effective technologies are scientifically and practically feasible. The types of strategic investments suggested below could accelerate translation of that theoretical feasibility into reality by fostering new collaborations, creating jobs first in academia and small biotechnology companies and then in national and global marketing entities as MPT products are commercialized.

The secretariat for the IMPT is the Coalition Advancing Multipurpose Innovation (CAMI), based at the Public Health Institute. CAMI is pleased, on behalf of the IMPT, to present the ideas below for consideration by the Obama Administration as part of the Office of Science and Technology Policy's Request for Information: *Building a 21st Century Bioeconomy*.

Grand Challenges:

Q1. The grand challenge for multipurpose prevention technologies (MPTs) consists of designing vaccines, contraceptives, microbicides and devices (e.g. intravaginal rings, diaphragms) that address multiple reproductive health needs, including prevention of unintended pregnancy; sexually transmitted infections (STIs), including HIV; and/or prevention of other reproductive tract infections (RTIs), such as bacterial vaginosis or urinary tract infections. While scientifically challenging, development of safe and effective MPTs is technically feasible (Hemmerling et. al., *Report of a 2011 MPT "Think Tank"*). Importantly, MPTs would increase efficiencies for end-users, as well as health care funders and providers, by providing simultaneous protection against multiple health risks, following the continuing trend in pharmaceutical development in general toward development of combination vaccines and therapeutic solutions.

The IMPT proposes that Grand Challenge Prizes for MPTs would be awarded for successfully meeting any number of the following near- term (2-3 years) and longer- term (4-8 years) challenges:

Near-Term Prize 1: ***Determine mucosal tolerance in the genital tract of women.*** Systemic priming followed by mucosal (oral or nasal) boosting is an effective route of the induction of both systemic and mucosal immune responses without the danger of inducing mucosal tolerance. However, this has not been demonstrated so far in the human genital tract.This study would have particular impact on immunization strategies that could prevent HIV and other STIs.

Near-Term Prize 2: ***Develop technology for the robust collection of product adherence data*.** A significant challenge for many HIV/STI prevention studies has been the assessment of end-user adherence to the study product. This prize would address this need and could be some type of electronic or chemical system used to accurately track compliant use of products during the course of clinical trials to allow for appropriate correlation between outcomes and product use.

Near-Term Prize 3: ***Develop at least one robust and predictive pharmacodynamics model for the assessment of MPT product efficacy*.** Typically, very large, expensive Phase 2b or Phase 3 trials are required to establish "proof of concept" – convincing evidence of preventive efficacy. The indications targeted by MPT products desperately and particularly need new, robust and accurate models which can be applied in early stage clinical trials to enhance the predictability of clinical outcomes in later-stage pivotal trials. Therefore, this prize would be awarded to the group or groups that can devise, develop, and validate robust human pharmacodynamics models that can be applied in the early phases of clinical evaluation to assist in product viability assessments and inform investment decisions.

Near-Term Prize 4: ***Develop a prospective, dynamic, and transparent instrument for assessing potential cost-effectiveness.*** The tool should allow developers and funders to iteratively assess the potential cost-effectiveness of MPTs as data become available during clinical evaluation and industrialization.

Longer-Term Prize 5: ***Develop a safe and effective (>70%) multipurpose systemic or mucosal vaccine for reproductive health.*** The vaccine should protect against two or more viral STI pathogens (HIV, HSV, HPV, HBV).

Longer-Term Prize 6: ***Develop a safe and effective (>80%) multipurpose vaginal product that prevents two or more STI/RTI pathogens, or prevents transmission of at least one STI pathogen and is also contraceptive.***

MPT Research and Development:

Q2, Q3 and Q4. The MPT field will not need to create new platform technologies, although it could well to do so, but is more likely to integrate promising, existing platform technologies that will be crucial to successful commercialization of MPTs and to a successful MPT-related bioeconomy. MPT investigators are currently utilizing a broad spectrum of industrialization platforms: chemical synthesis (hormonal contraceptives, antivirals), biotechnology (e.g.,subunit, live, and DNA vaccines, biopharmaceutical microbicides), delivery technology (e.g. intravaginal rings, bacteria, cervical barriers).

Because mucosally-active products for infectious disease indications are a small percentage of antibiotic/antivirals and vaccines, novel and effective MPT-related technology may be relevant to other mucosal infectious disease indications and inflammation. Further, drugs that are restricted to the mucosa would not be drivers of resistance if the virus is not replicating in mucus

Because MPTs are intended for large, cost-sensitive markets, the development and commercialization of these products could have a significant impact on the bioeconomy by broadening market opportunities for other drug products that have been limited so far by cost and scale of production.

Moving MPT Innovations from Lab to Market:

Q5. The primary barrier to MPT innovation is the failure of product developers to create new technologies that simultaneously prevent unintended pregnancy and individual or even multiple STIs. Each of these fields continues to operate autonomously with little coordination or cross-fertilization, despite the obvious synergies.

The Coalition Advancing Multipurpose Innovations (CAMI) guides a global initiative connecting science, industry and education to address the development and introduction of MPTs. The **Initiative for Multipurpose Prevention Technologies (IMPT)** is technology based (i.e., evidence-based science is at the core) and market driven. The IMPT provides a platform for product developers, researchers, donors/sponsors, advocates and clinicians working in sexual and reproductive health to coordinate their efforts and facilitate interdisciplinary research. This interdisciplinary approach provides an opportunity to integrate basic science with behavioral research and market analyses across the entirety of the Critical Path. Such an integrated process could be realistically expected to accelerate time to commercialization, at the same time insuring arrival at MPTs that are safe, effective, acceptable and accessible.

Q6. The **NIAID-AT-SBIR** (the National Institute of Allergy and Infectious Diseases- Advanced Technology-Small Business Innovation Research) program has two milestone-driven phases and appropriate funding (Phase 1 is $600K over two years; Phase 2 is $3M over three years) that could catalyze MPT development if they were a program priority. A study of innovation (Block and Keller 2008) suggests that SBIR-nurtured companies consistently account for a significant fraction of US innovations -- a powerful indication that the SBIR program has become a key force in the innovation economy of the United States. An **MPT-prioritized NIAID-AT-STTR** (Small Business Technology Transfer) program oriented towards academicians could create jobs in universities and non-profits (public health, engineering, clinical trial design and conduct, statistics), and for-profit companies. Equally- funded programs focused on contraceptive development (i.e. a new NICHD-AT-SBIR/STTR) could catalyze the development of new methods for pregnancy prevention.

The current, overarching drug development paradigm is for lead products to be developed by small firms which then partner with large firms for commercialization. Consistent with this paradigm, small innovative firms developing MPTs would be a vehicle for leveraging private-sector funding and thereby having a significant impact on the bioeconomy.
Q7. The MPT field would not require the release of any high-value data by the US Government.

Q8. Approximately two thirds of U.S. innovations involve some kind of **inter-organizational collaboration --** a situation that reflects the more collaborative nature of the innovation process

and the greater role in private sector-innovation by government agencies, federal laboratories, and research universities (Block and Keller 2008). Innovative mechanisms used at USAID and NIH/NIAID (e.g. NIAID's Integrated Preclinical/Clinical Program, U19) that promote a focus on product development and initial clinical trials have been critical to date. Additional programs funded by governments, non-profits and/or for-profits that are oriented around product development (i.e. the safety, efficacy, and industrialization dimensions of the Critical Path) would be undeniably desirable in the future.

Industrialization remains a major risk for the development and commercialization of products (FDA 2004), and is fundamental to the success of the Bioeconomy. Problems in physical design, characterization, manufacturing scale-up and quality control routinely derail or delay development programs and are often rate-limiting for new technologies. MPTs provide a conceptual platform that stimulates innovations for technology platforms, especially manufacturing. Funding rapid, versatile and cost-effective manufacturing systems that are amenable to an iterative process will be crucial for MPT development.

Workforce and MPT Development:

Q9. Professional training programs in a variety of fields should encourage multi- disciplinary collaboration for the creation of MPTs. The natural sciences (chemistry, biology) and bioengineering are, necessarily, intimately involved in creation of new technologies. Equally important is the rollout of new technologies through advocates and program implementers with expertise in international development, public health, sociology and behavioral science. The new field of MPTs will engage all of these fields.

Q10. Community colleges can play a key role in the development and rollout of MPTs, by preparing cadres of pre-professionals trained in the biological, clinical, social and implementation sciences.

Q11. The private sector must play a key role in the conceptualization, creation, testing, and rollout of new MPTs. The ultimate goal of the field is to produce one or more commercially viable technologies that can be disseminated globally by commercial interests. While the potential commercial benefit for such a universal set of products is enormous, the financial and regulatory barriers to creating and testing them will drive the private sector to seek opportunities for collaboration and partnerships.

Q12. While some MPTs are advancing through human studies, others remain purely theoretical or on the drawing board. That said, there remains ample opportunity for the conception of new technologies that fall within existing paradigms (barrier methods) as well as more advanced technologies (vaccines and injectables). Government, industry and academia can separately incentivize research in this area.

Reducing Regulatory Barriers for MPTs and the Bioeconomy:

Q13. If the IMPT is to deliver on its promise, scientific creativity and effort must focus on improving the product development process itself, with the explicit goal of robust development pathways that are efficient and predictable and result in products that are safe, effective, and accessible (FDA, 2004). The IMPT must modernize the critical development path that leads from scientific discovery to end users.

A new product development toolkit — containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product.

The development of MPTs faces similar challenges as other global health initiatives (Bollyky 2011), i.e. two substantial bottlenecks threaten the IMPT's capacity to commercialize products. First, there is not enough clinical research and regulatory capacity in many settings to support the clinical trials that need to occur there in order to complete the development of these products. This lack of regulatory and clinical trial capacity can undermine the safety of subjects and the validity of clinical data. Second, even with expected attrition in the pipeline, current levels of financing are insufficient to support the clinical development of these products under current cost assumptions. Addressing these related challenges will require not only identifying new sources of funding for large-scale clinical trials and capacity building—but also devoting more attention to how these trials and their regulatory pathways can be improved to reduce unnecessary costs, delays, and risks to trial subjects.

Q14 and Q15. The IMPT recommends a two-pronged strategy to bring the costs, risks, and finances for clinical trials for MPTs into a more sustainable balance.

First, establish regional mechanisms for the regulation and ethical review of clinical trials. Moving to a single, integrated process by which clinical trials occurring in multiple countries and sites are approved and overseen would improve the coordination and pool the capacity of ethics committees and national regulatory authorities (NRAs) involved, reduce regulatory inconsistencies and overlap, and provide a more attractive platform for external assistance and donor support. In doing so, regional cooperation would offer the opportunity to improve regulatory capacity and reduce clinical trials costs at fairly low expense to donors and local governments.

Second, better/faster/less expensive clinical trials are needed. Achieving that objective will require a focus on the key parameters and objectives of the trial, evidence-driven approaches, and early engagement among trial sponsors, investigators, and NRAs. Strategies may include:

- *Adaptive study designs for licensure; more support for policy research in phase IV studies.* Focusing pivotal trials on the research necessary to support licensure would reduce costs, expedite product registration, and lower site and investigator demands. For this approach to succeed, however, donors must increase funding for the phase IV *policy and epidemiological studies.
- *Early investigator input and independent advisory committees*. Local investigator and independent stakeholder input should be solicited early in study and protocol design to help spot potential problems and help keep studies simple, feasible, and focused.
- *Pressure-testing protocols.* "Pressure test" protocols and screening criteria by performing them with potential subjects and study products prior to enrollment. This approach improves the efficiency of trial design, reduces the number of subsequent protocol amendments, and ensures recruitment of appropriate subjects into clinical trials.

A New Model for Product Development Partnerships:

Q16. The IMPT seeks to create an environment conducive to self-organizing, decentralized product development partnerships. Existing NIH funding mechanisms that support this integrated approach (e.g. U19s, R21/R33, R43/R44) are desirable for MPTs.

Q17. MPTs represent a uniquely high-impact opportunity or pre-competitive collaboration in life science research and development. This work can and should be informed by successes achieved in the development of many multiple-indication technologies and medicines, including vaccines.

Conclusion:

The IMPT thanks the Administration for offering this opportunity to provide a response to the Office of Science and Technology Policy's Request for Information. We believe that MPTs offer a strong case for a lifesaving technology with the potential for direct impact on the lives of half of the planet's population, as well as a chance for the Administration to demonstrate a commitment to game-changing innovation. The MPT field is poised to become one of the great technology success stories of the 21st century. With a small strategic investment now, the Obama Administration can assure its own place in the history of that dramatic moment, while creating economic and job opportunities through the fields of biotechnology, engineering, manufacturing, international development, and marketing.

References:

Block F and Keller MR. Where do innovations come from? Transformations in the U.S. National Innovation System, 1970-2006. The Information Technology and Innovation Foundation (2008).

Bollyky T (chair). Safer, Faster, Cheaper**:** Improving Clinical Trials and Regulatory Pathways to Fight Neglected Diseases. Report of the Center for Global Development's Working Group on Clinical Trials and Regulatory Pathways. (2011).

FDA. Challenge and Opportunity on the Critical Path to New Medical Products. (2004).

Hemmerling A., Harrison P., Young Holt B., Manning J., Stone A., Whaley K. Advancing the Scientific and Product Development Agenda. Report of an "MPT Think Tank". Washington. DC, USA. (2011).

Response to RFI concerning the President's Blueprint for the Bioeconomy

Submitted by: Aprile L. Pilon, Ph.D.
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Responses to questions in order:

1. Grand Challenges: The greatest challenge in biomedical science today that will have a tremendous impact on healthcare and long term healthcare costs is in learning to manipulate the human immune system. The immune system is the key to curing cancer, autoimmune disease, responding to infectious diseases, asthma & allergy, even affecting long term remodeling processes. If you have to pick a single focus, it should be to first develop the tools to study the human immune system (animal models, in vitro platforms- reconstituted elements of the immune system, in silico response simulations and predicting immune phenotype based on genotype, and finally safe human testing methods). This is very hard to do and has not been done well so far. Other than vaccine technology, which despite decades of use and research, is still not an exact science, we know very little about how to manipulate the immune system to create a therapeutic benefit. I am developing an immunomodulatory drug and this is a very difficult and underfunded field.
2. High throughput approaches are not the be-all end-all solutions. At the present time there is a glut of information from the Human Genome Project that we are still sorting through to create diagnostic and therapeutic products. It will take decades to mine the information we already have. Funding should be made available for meritorious high impact individual projects through programs like the NIH Cures Acceleration Network.
3. X
4. Commercialization of recombinant human protein therapeutics and diagnostics made possible by the Genome project will require market exclusivity to justify investment. Since the project was completed in 2000 and all sequences disclosed publically or included in massive composition of matter patent filings that no one can develop in 20 years, there is an issue with lack of strong IP coverage for most of the potential products to be derived form that project. To address this issue will require a paradigm shift in the US – suggestions as follows: extend patent coverage for at least 7-10 years post FDA approval and enforce the 12 years of biologics market exclusivity in the Healthcare Reform act.
5. Funding is the main barrier to product development. Academic labs typically lack a fundamental understanding of the drug development process AND are not motivated to develop products as company personnel are motivated. (The academic product is the publication and the mission is not commercial.) The SBIR program and CAN should be receive greater level of funding through NIH. At the same time, NIH needs to maintain the clinical research infrastructure in academic and medical school settings to provide an environment in which to test new products.
6. Triple the NIH SBIR program immediately!

Clarassance, Inc. Aprile L. Pilon, Ph.D.

An Entrepreneurs Recommendations based on first-hand experience
November 2011

As a 17 year veteran of the biotech industry, having participated in 5 start up biotech companies, I make the following recommendations based on first-hand experience of the issues faced by companies developing biologic drug products that require protracted development and approval processeses.

I. **Increase funding for the FDA Orphan Products Grant Program**. These grants are for "shovel-ready" drug development projects for drugs that must have already received orphan drug designation (requiring in depth knowledge of the disease condition and market) and must have an active Investigational New Drug Application.

An enormous amount of credit for the development of the entire biotechnology industry should be given to the Orphan Drug Act and the Orphan Product Grant Program. Biotech drugs like erythropoietin (Amgen), human growth hormone (Genentech), and Ceredase (Genzyme) would, arguably, never have been developed if not for the act and the grant program. Patent protection was not possible for many of the first biologic drugs because their compositions and uses were in the public domain before it became possible to produce them recombinantly and thus feasible to produce sufficient drug product to serve their patient populations. These biologic drugs were too risky to invest private capital in and the orphan product grant program provided the critical funding for early clinical trials. Thus, the Orphan Drug Act and the Orphan Product Grant Program are responsible for generating thousands of high paying jobs, enabling the growth of several multi-billion dollar companies, building enormous value in the capital markets, in the biotechnology industry over the past 40 years, not to mention the millions of patient lives positively impacted by the products supported by the program.

The Orphan Product Grant Program budget has been nearly flat since 1995, when it was $12 million in the program budget, through the 2012 budget for which $14M has been allocated. The budget has remained at $14M for the past 5 years, while the number of grant applications has at least tripled from 30-40 in 2007 to well over 100 in 2010 and 2011. Only 10-15 new grants per year can be funded, a success rate well below that of NIH academic grants, during a time when more company and product development grants should be funded. For the relatively small grant investment (up to $400K/yr for up to 4 years, $1.6M total), a large increase in product value may be realized.

The FDA is the only government agency well-suited to administer this program because it is intimately familiar with the issues and challenges encountered during drug development. No other government agency can serve this function. The FDA Office of Orphan Product Development (OOPD) understands the urgent need to develop therapies for rare conditions and takes an active role in supporting and monitoring the clinical trials that are sponsored by the grant program, even advocating for these trials with other divisions within FDA. As a result of OOPD's involvement, the success rate for gaining approval is significantly higher than for drugs outside the program.

For these, and many other reasons[A], we strongly recommend that the budget for the orphan product grant program be expanded immediately to $30M for 2012. We understand that this is up to the discretion of the Agency and urge that FDA does its part to stimulate the economy.

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A. Rare Diseases and Orphan Products: Accelerating Research and Development. Marilyn J. Field and Thomas F. Boat, Eds.; Institute of Medicine of the National Academies. The National Academies Press (Washington, DC.) (2010).

II. Determine whether FDA or Dept of Commerce is supposed to enforce the 12 year post-approval period of exclusivity for biologic products (**Healthcare Reform Act of 2010**; HR3590, Section 7001-7003, pp 1860-1906). **Accelerate release of guidelines for what the new law means and how it will be enforced.**

"We can't wait!"

A significant period of post-approval market exclusivity is required for these types of products in order to incentivize and obtain the investment required to develop them. The development of orphan drugs without patent protection has shown that a period of at least 7 years of market exclusivity is required before an investment will be made in drug development. In my own discussions with large pharmaceutical companies, they want at least 10 years of post-approval market exclusivity to incentivize the required investment in product development, 12 would be better. Note that most business development people at large pharma companies aren't even aware of this legislation. They will not pay any attention to it until FDA issues guidances on enforcement. Small biotechnology companies with outstanding biologic products that are short on patent life, like mine, can't wait months or years to get an answer from the FDA on how, or even whether, they will enforce the new law. It is unacceptable that promising products, some that have even advanced into the clinic and demonstrated efficacy in some instances, are abandoned, and don't receive the investment required to gain regulatory approval and make it into the marketplace. Conversely, inferior products with more recent patent claims may receive the resources to be developed. In the worst case, promising products with short patent life may be modified for the purpose of creating a new patentable composition and not necessarily to improve product performance, which could ultimately increase the likelihood of hypersensitivity reactions or otherwise compromising safety. It is a disservice to the American public to be denied the best therapies due to arbitrary patent deadlines which were never intended to have been applied to modern drug products requiring lengthy testing and approval processes. Failure to invest in partially development products represents a senseless loss of investment capital that discourages further private investment in the biotechnology industry. The clarification and subsequent enforcement of this exclusivity period for novel biologics will enable the investment required to advance promising products for which the limit of patent protection is insufficient.

III. **Increase the period of market exclusivity for first to market (eg. first to approval) drugs and devices from the current 5 year period to a minimum of 10 years (like Europe)**. This applies to

all drugs, not just biologics. Chemically synthesized drugs are generally less expensive to produce and it is typically less expensive to develop synthetic processes for chemical drugs than for biologics, hence the shorter period of exclusivity. Due to the protracted timelines for development of regulated biomedical products, patent life is often insufficient to provide any period of market protection once the product has been approved for market by the FDA. This minimum period of market exclusivity enables corporations and investors time to recover their investment and return a profit on the enormous investment required for these types of products to reach the marketplace.

There is no published rationale for the number of years required to recoup investment made in product development and clear a reasonable profit. Product valuation models are unique to each company or investor and there are a tremendous number of variables that can drastically alter projections of product development costs and eventual profits from marketed products. However, there is no question that the number of years of exclusivity must increase from five in order to stimulate investment in new product development. Other jurisdictions, like Europe and Japan, allow 10 years of market exclusivity for first-to-market, first-in-class drugs. Given new requirements for post-approval safety monitoring programs now required by FDA (REMS), which are projected to cost up to 6% of the net sales to comply with, 10 years should be a minimum.

IV. Increase and strengthen the SBIR program at NIH to stimulate innovation in biotechnology and biomedical product development. I am a founder of the Small Biotech Business Coalition (www.smallbiotechcoalition.org) and I cannot emphasize how important this program.

V. Appropriate funding for the NIH's Cures Acceleration Network to provide funds to develop therapeutic products.
VI. Provide greater tax incentives not only for companies developing pediatric drugs but also to their investors, including new drug testing in children AND reformulation of existing drugs (approved in adults) for pediatric populations. The FDA has a carrot and a stick for companies developing drugs for children (Best Pharmaceuticals for Children Act, 2002), but it's not sufficient to incentivize the investment required for pediatric drug testing.
VII. Extend patent protection for 10 years AFTER regulatory approval is obtained for all drugs and biologics.

I would be happy to address any questions you may have about this response. Please feel free to contact me.

Sincerely,

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Office of Government Affairs

Response to Request for Information: Building A 21st Century Bioeconomy

Tulane University

December 6, 2011

(1) Grand Challenges for the Bioeconomy

The identification of Grand Challenges must represent an interactive and collaborative process that incorporates input from individual university-based researchers and senior administrators, together with Federal agencies, and industry. Among the nation's grand challenges that are currently being addressed, Tulane University has been particularly focused on **(a) Biomedical and Bioengineering Research**: continued development of its rapidly emerging Biosciences Corridor; and **(b) Coastal Restoration, Environmental and Ecological Research:** research and development related to Gulf of Mexico coastal restoration and protection of related wetland and energy resources that drive the state's economy.

(a) Biomedical and Bioengineering Research: Advances in health care are built upon the foundation of academic biomedical, biological, and bioengineering research. Continued federal support in those core research areas is essential for the success of current and ongoing private and state investments in the New Orleans Biosciences Corridor. Examples of recent area investments include:

- New Orleans BioInnovation Center
  Status: Open & Operating. Completed: June 2011. Size: 66,000 square feet of state-of-the-art wet-lab, office and conference space. Cost: $47 million. To house biotech and life sciences entrepreneurs and startups, as well as support research at four area universities; housing about 200 employees from 80 companies at full capacity. Critical link that turns university research into privately commercializable enterprises. Five biotech start-ups and two venture captial firms have already moved into the building, and twelve more are on the way
- University Medical Center
  Status: Site preparation work, construction to begin by year end. Completion: April 2011/2015. Site: 34 acres. Size: 2.2 million square feet, 424-bed public hospital. Cost: $1.09 billion; state lawmakers approved funding September 2011. Jobs: 5,280 new and saved jobs over first five years. Part of collaborative complex with the new VA Medical Center (see above). Both will be key academic anchors for LSU, Tulane, Dillard, Xavier, SUNO, Delgado, and others throughout South Louisiana
- Louisiana Cancer Research Center

Status: Under Construction. Completion: Year End 2011. Size: Shared 175,000 square-foot, 10-story facility. Cost: $90 million. Developed by a partnership among LSU Health Sciences Center, Tulane University, Xavier University of Louisiana, and Ochsner Health System

- Veterans Affairs Medical Center
  Status: Under Construction. Completion: June 2011/Late 2014, full activation 2015. Site: 30 acres. Size: 1.6 million square feet; 200-bed complex will serve over 70,000 enrolled Veterans. Cost: $995 million construction budget (fully funded). Jobs: 1,100 new employees
- Ochsner Health System
  Relocating 500 to 750 employees to the CBD during the 1st Quarter 2012
  Moving executive, corporate and business functions (no medical care)
  80,000 square feet on top 4 floors of the Benson Tower (enough room to grow to 1,000 employees)

(b) Coastal Restoration, Environmental and Ecological Research: Continued federal support for basic and applied ecological and environmental and societal research is essential for the survival and growth of two of the key economic drivers of the Gulf States: the seafood industry and energy production. University-based research in core disciplines supporting those economic drivers is rapidly growing and expanding among all of the Gulf Coast States.

(2) Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy.

- It is essential that traditional life sciences and basic science research be integral components of the new bioeconomy blueprint.
- Federal funding priorities should not neglect the importance of investing in high-risk – high reward research, including individual investigator-initiated research as well as problem-driven multidisciplinary collaborative research and development driven.
- Federal investments in critical infrastructure are of particular importance. These include programs that provide essential funding for construction, renovation, and major equipment, in addition to support for research graduate students, postdoctoral researchers, and emerging research faculty. One of the major challenges facing research universities today is recruiting and retaining motivated and energetic graduate students and faculty.

(6) Changes to Federal SBIR and STTR Programs.

- States like Louisiana that are aggressively investing in new infrastructure in order to enhance their abilities to compete in the areas of biological and biosciences technology and innovation struggle to navigate the existing SBIR and STTR programs that tend to require already existing local industry capabilities and ties. We would suggest that the Administration establish additional support mechanisms, including workshops and other outreach, to bolster SBIR/STTR competitiveness specifically in EPSCoR states in order to promote the development of new bioeconomy tools.

(9) Workforce Development.

- Attracting and retaining qualified graduate students, postdoctoral researchers, and research faculty to careers in biological and bioscience fields is one of the major challenges facing U.S. universities today. Existing programs such as the NSF Integrative Graduate Education and Research Trainee (IGERT) Research Traineeship, and Grant Opportunities for Academic Liaison with Industry (GOALI) programs, and the NIH Centers of Biomedical Research Excellence (COBRE) program are extremely important resources that facilitate the training and development of scientists and engineers and foster the skills needed for the bioeconomy workforce. Additional or enhanced programs that help universities in their efforts to mentor emerging faculty, postdoctoral researchers and graduate students from all scientific disciplines in order to accelerate their integration into the bioeconomy workforce are needed.

Submitted by:

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Office of Government Affairs
Tulane University

Association of Independent Research Institutes (AIRI) Response to RFI on National Bioeconomy Blueprint

The Association of Independent Research Institutes (AIRI) welcomes the opportunity to provide input on the President's National Bioeconomy Blueprint. The Blueprint recognizes that biological research is an important economic driver, and we applaud the White House Office of Science and Technology Policy (OSTP) for seeking feedback from the research community to maximize the nation's federal research investment. AIRI is a national association of more than 80 independent, not-for-profit research institutes whose primary mission is research. Our relatively small size and greater flexibility provide an environment that is particularly conducive to scientific creativity and innovation. Independent research institutes receive 10 percent of the National Institutes of Health (NIH) peer-reviewed, competitively-awarded extramural grants. On average, AIRI members receive over 10 percent of their funding from the National Science Foundation (NSF) and nearly half of AIRI member institutes receive Department of Defense (DOD) funding.

Independent research institutes often partner closely with neighboring universities and complement their research by targeting specific disease or conditions. In some parts of the country, AIRI member institutes are primary contributors to local and regional economies through job creation and investment in innovation and discovery. It is important to note there is not just one bioeconomy, but rather many layers from international trade and commercialization, to regional efforts and the local research institution. AIRI members have leveraged their roles in the bioeconomy by developing strong partnerships with industry and the federal government to help translate basic research discoveries into applications that improve health and health care.

Grand Challenges

Addressing grand challenges requires an interdisciplinary approach that includes the work of individual researchers, as well as the collaborative approaches of large multidisciplinary centers. Members of AIRI are some of the top recipients of center grants and awards that encourage interdisciplinary collaborations. Independent research institutes operate important centers and core facilities that are supported by NIH center awards and provide essential scientific services to researchers across the country. These centers are research hubs that provide efficient services and enable essential research across many disciplines.

To tackle the biggest research challenges in health, the federal government should develop initiatives that encourage the coordination of existing research among universities, industry and non-profits. These "bioeconomy consortia" could maximize the impact of federally-funded research in specific priority areas set by the Administration. AIRI member institutes have considerable experience working closely with universities and industry, and have found these partnerships essential to moving cutting-edge research into the marketplace.

Research and Development
Traditional life sciences and basic research are central to the nation's bioeconomy and consequently should be predominately featured in the National Bioeconomy Blueprint. As noted earlier, federal funding priorities should include supporting truly interdisciplinary projects. As we enter an era of large-scale projects and multi-disciplinary research, there is a need to ensure that high-risk, high-reward ideas are also supported. However, make these advances possible, continued strong support for basic research is vital as it provides the necessary foundation.

During times of budget constraints, cuts are inevitable, but intermittent funding is particularly destabilizing for science as it is a constantly evolving cycle that depends on previous discoveries, as well as failures. Also, stable and sustained funding for research helps generate the talent base for the researchers of the future. A continued federal investment signals to young scientists the inherent value of their work and helps independent research institutes retain talented investigators.

Moving Life Sciences Breakthroughs from Lab to Market
For specific examples of AIRI member institutes bringing research discoveries into clinical practice and the marketplace, see the attached compilation of AIRI translational research success stories. These are stories of research conducted by independent research institutes and the resulting drug, therapy, diagnostic company or prevention method, as well as the impact on health and health care. Many of these examples highlight companies and other research collaborators, as well as the federal funding that enabled the translational research.

AIRI member institutes would like to be more competitive in the Small Business Innovation Research (SBIR) program, but due to their small size and faculty pool, some of our member institutes find it difficult to meet requirements. More flexibility in the SBIR program for proof-of-concept funding or pre-incorporation activities would allow AIRI members to engage more fully in this activity and bring to the program our considerable experience in working with start-up and small biotech companies. Additionally, allowing Small Business Technology Transfer (STTR) program funds to be used for proof-of-concept programs would replicate success of organizations and approaches such as the Coulter Foundation, in which individual and institutional funding are subject to rigorous evaluation by panels of local experts in translational and proof-of-concept research. These programs have the potential to help move discoveries more effectively and efficiently into the marketplace. More attention to the need for early-stage, proof-of-concept research would certainly improve their success.

Regulatory Barriers
It is essential the Administration continue its efforts to ensure government regulation does not stifle innovation, particularly in the realm of encouraging public-private partnerships. AIRI appreciates that the recently finalized NIH conflicts of interest rule does not impose burdens and requirements that could have had a negative effect on collaborative relationships between universities and industry. As federal agencies continue efforts to regulate potential conflicts of interest, care must be taken to not inadvertently discourage appropriate interactions among research faculty, institutions, and industry. While conflicts of interest must be closely monitored, an emphasis on elimination, rather than management, could produce a chilling effect on research institutions' ability to develop important partnerships and on the Administration's efforts to increase commercialization.

As noted by NIH Director Francis Collins, there are significant layers of reporting and burden that can impede research by consuming valuable and limited resources. For example, effort reporting requires additional personnel and forces scientists to spend many hours accounting for their time, rather than

conducting research. The data and information developed by effort reporting is of very little value to the federal government and certainly does not advance scientific research. Additionally, with so many federal funding opportunities requiring collaboration between multiple partners, sub-recipient regulations must be streamlined to reduce burdens and time spent on paperwork.

Finally, it is imperative that the federal government take specific steps to improve the predictability and transparency of the regulatory system, including assuring that research cost policy rules are applied fairly and consistently across the country. For AIRI member institutes, the disparities in how the Office of Management and Budget (OMB) Circular A-122 principles are applied by the Department of Health and Human Services (HHS) Division of Cost Allocation (DCA) field offices causes significant confusion and disadvantages some institutions for no apparent reason. We continue to work with DCA regional offices on this issue and hope the Administration encourages transparency in this area.

Conclusion

AIRI appreciates the opportunity to contribute ideas to the National Bioeconomy Blueprint. Our institutions' research-focused mission and relative small size position us as strong partners with industry, universities, and the federal government. We play prominent roles in the nation's biomedical and behavioral research enterprise and are proud to make vital contributions to fields including cancer and AIDS research, aging, genomics, neuroscience, and public health awareness. For additional information, please contact Erica Froyd in the AIRI Washington Office at [redacted].

NATIONAL POSTDOCTORAL ASSOCIATION
www.nationalpostdoc.org

National Postdoctoral Association Response to OSTP RFI: Building a 21st Century Bioeconomy

On behalf of the National Postdoctoral Association (NPA), we would like to thank the President and the White House Office of Science and Technology Policy (OSTP) for the opportunity to provide information during the development of the National Bioeconomy Blueprint. The NPA is a 501(c)3 nonprofit, professional association that seeks to provide a national voice for postdoctoral scholars (postdocs), to educate the public regarding the contributions that postdocs make to U.S. innovation and discovery, and to facilitate positive change for these new researchers. Since our founding, we have worked collaboratively with all stakeholders to enhance the postdoctoral experience and thereby to maximize the effectiveness of the U.S. research endeavor.

Because of our organization's expertise in and focus on postdoctoral scholars, this response is limited to questions regarding workforce development, namely questions #9 and #11. It should also be noted that this response focuses specifically on the postdoctoral experience, although some of our suggestions are also relevant to other populations such as graduate students.

(Question 9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Educate Principal Investigators (PIs)

(Please note: the term Principal Investigator (PI) is being used in this response to signify not only PIs but also faculty mentors and supervisors, where they are not one and the same.)

The NPA's interactions with postdocs suggest that the majority of new biomedical scientists begin their postdocs with high hopes that their Principal Investigators' (PIs') connections and expertise will help them to acquire that elusive tenure-track position, in spite of statistics that suggest that across all disciplines only one in four new Ph.D. recipients will acquire such a position. To compound this situation, PIs more often than not perpetuate the cultural norm that the ultimate goal for an independent researcher is academic tenure. There are several possible reasons for this break with reality on the part of both postdocs and PIs, but the most likely reason, aside from traditional expectations for a successful scientific career, is that neither party truly understands that there are no longer enough tenure-track academic positions to go around, given the continued growth in the number of postdocs. **Institutions need to educate PIs about the economic reality in the life sciences.** At the very least, institutional leaders of career development/training programs need to provide PIs with data

describing the current job market for doctorate recipients in the life sciences. Currently, many postdocs feel like a "failure" as a scientist if they do not acquire a tenure-track academic appointment, and many PIs feel like a "failure" as a mentor if their postdoctoral trainees do not move on to a tenure-track academic appointment. Education about current job market realities is needed to change these cultural misperceptions.

In addition to providing education about the general economic landscape, training programs also need to educate PIs about (1) the types of jobs in the private sector that are available to postdocs and (2) the skills necessary to succeed in those jobs. In today's environment, it would be preferable for PIs to encourage postdocs to consider all of their career options. Yet, in reality, most PIs only understand the academic career track. Institutions and departments need to inform their faculty members about the non-academic career options open to doctorate recipients and the types of skills their trainees need to develop in order to secure those jobs. It would also be helpful for institutions to provide resources or training that would allow PIs to be better informed about the job search process in the private sector and the ways in which it differs from the job search process in academia. Without this type of information, even well-intentioned PIs might be at a loss about how to mentor and prepare postdocs who intend to pursue careers in the private sector. Federal granting agencies could support the efforts of local institutions by developing resources that institutions and departments can use to educate their faculty members.

The importance of the postdoc office cannot be underestimated in terms of providing this information not only to PIs but also to postdocs. Since its establishment, the NPA has encouraged and actively supported the establishment of postdoc offices at research institutions, and the number of postdoc offices known to the NPA has increased from 13 in 2000 to 128 this year. The presence of an office, even if it is just one part-time person at a desk in the graduate dean's office, results in new or increased development of resources and adoption of institutional polices that support postdocs. Postdocs become more visible to faculty as colleagues and contributors to the institution's research efforts. **Thus, the establishment of postdoc offices should be at the minimum endorsed by federal agencies.**

Raise Mentoring Expectations

The PI holds a tremendous amount of power over a postdoctoral researcher. His/her supervision and mentoring (or lack of same) can make the difference between success and failure for the vulnerable postdoc. **Along with providing appropriate education and training for PIs, institutions, departments, and training programs need to raise their mentoring expectations of PIs and enforce those expectations. At a minimum, PIs should encourage postdocs to (1) consider all of their career options; (2) find multiple mentors as needed who can guide them in those options; and (3) pursue professional development opportunities.** PIs should support and consider postdoc offices as a resource, rather than as another layer of bureaucracy. Institutions should communicate these expectations clearly to PIs, and the fulfillment of these expectations should be considered during the tenure process and other evaluations.

Considering the policies of federal funding agencies, however, there is currently little incentive for local institutions to raise expectations of PIs and encourage better mentoring of trainees with an interest in non-academic career paths. **To ensure that mentoring expectations of PIs are raised, it is critical that federal funding agencies make several policy changes to support the efforts of local institutions:**

1) **Federal funding agencies should provide stricter guidelines and expectations for the role of the PI in supervising postdocs and the role of the institution in**

supporting the PI and the postdocs. At the minimum, all federal funding agencies should require a mentoring plan for all postdocs supported by them, including those on research grants. The NSF recently implemented such a requirement after the passage of the 2007 America Competes Act. Agencies should also include the evaluation of the postdoctoral mentoring plan as part of the peer review process and require reporting on the outcomes of that plan in annual reports. Agencies should also gather data from postdocs themselves about the perceived effectiveness of the mentoring plans.

2) **The NIH needs to clarify the definition of "success" for institutional training grants and to make a significant and ongoing effort to educate its reviewers and personnel regarding acceptable outcomes in regard to employment of trainees.** Although the current wording in the solicitation is broad enough to include independent research careers in industry, government, and other fields as well as academia, the workforce culture is such that wording like "productive scientific careers" is interpreted by the reviewers and PIs as "productive [academic] scientific careers." (The NPA has been given to understand that this interpretation was not intended by the NIH.) The NIH could help to change the culture by including specific wording that clearly states that independent research careers outside of academia are equally acceptable indicators of training "success."
3) **Furthermore, the NIH and other federal funding agencies should consider broadening the definition of "success" for training grants to include "science-related" positions.** The NPA understands that doing so would enter a gray area of "What is science-related?" but believes that it should be seriously considered, given the lack of independent research positions today. Without these changes to the definition of successful training outcomes in the evaluation of grants, training programs and PIs that do take efforts to mentor and prepare postdocs for a variety of private sector bioeconomy careers will be at a disadvantage during the grant review process.

Utilize Core Competencies to Provide Relevant Self-Assessment and Professional Development

The variety of career options available today demands a diverse array of skills, such as writing grant proposals and CVs or mastering the principles of effective resource management, that are often neglected during doctoral study and postdoctoral research. The postdoctoral experience will be more relevant to career and professional development if the scholar seeks or is offered opportunities to acquire, maintain, or improve such skills. The NPA has established six broad core competencies meant to serve primarily as: (1) a basis for self-evaluation by postdoctoral scholars and (2) a basis for developing training opportunities that can be evaluated by mentors, institutions, and other advisors (www.nationalpostdoc.org/competencies). **Individual institutions and training programs should adapt the NPA (or other) core competencies and develop discipline-specific core competencies that are used to standardize their training efforts and evaluate the effectiveness of their training programs.**

Federal agencies can encourage these efforts by developing agency-wide core competencies to guide the formal and "informal" training (on research grants) of biomedical postdocs. In some respects, the NIH has already begun to do so in the training program language (e.g., requirements for training in responsible conduct of research). The federal government can also encourage these efforts at institutions by allowing funds from current institutional training grants to be used for the development of core competencies.

Provide Opportunities for Diverse Professional/Career Development and Career Exploration

Institutions and training programs should develop and provide workshops, seminars, and other programs for postdocs that (1) encourage career exploration and (2) help postdocs develop the skills necessary for success in private-sector jobs. Postdocs rarely receive training in business concepts and soft skills (e.g., teaching, leadership, and management) that would help them succeed in the private sector. They could benefit greatly from access to business school courses, and institutions without business schools should be encouraged to offer workshops and seminars that offer training in management, interpersonal communication, and basic business concepts. Postdocs from other countries conducting research in the United States would often benefit from English language training to ensure that their language and communication skills are sufficient for the needs of private sector employers. In addition, many postdocs are unaware of the variety of private sector jobs available to them, and postdoctoral training programs could provide opportunities for career exploration that would allow postdocs to determine if they would be a good fit for one or more private sector career paths. Postdoc offices do and could provide coordination and leadership of these efforts.

In addition to providing funding to institutions and training programs for the development of such activities and programs (through institutional training grants and similar funding mechanisms), the federal government could support the efforts of institutions by providing a mechanism for institutions to share information with each other about particularly innovative and effective career development programs and activities. Federal funding agencies could also provide centrally produced career development activities to support local efforts. Funding agencies would not necessarily have to "reinvent the wheel" but could build upon or expand the dissemination of the resources that have been developed by the NIH Office of Intramural Research, the NPA, and other groups. For example, funding agencies could encourage institutions to use mentoring tools such as individual development plans [such as that developed by the Federation of American Societies for Experimental Biology (FASEB)] and the Association of American Medical Colleges (AAMC) Compact between Postdoctoral Appointees and Their Mentors.

Allow Release Time for Professional Development on NIH Research Grants

In order for postdocs to be able to take advantage of any additional career exploration and career development opportunities developed by local institutions and training programs, **it is critical that the NIH require release time for postdocs funded through its non-training grants to take advantage of these career development opportunities.** Currently, many PIs will not allow postdocs to take time to develop soft skills because of the 100%-time-and-effort required by most NIH grant guidelines. Building in from 5% to 20% release time for postdocs to pursue opportunities to build these skills will help to prepare them for diverse careers. Rather than take away from productivity, this time will help them to be more productive and help to ensure their future productivity and success[1]. Without this change in NIH policy, it is likely that any new training resources developed by local institutions and training programs will be poorly utilized.

[1] "Postdocs reporting the greatest amount of structured oversight and formal training are much more likely to say they are satisfied, to give their advisors high ratings, to experience relatively few conflicts with their advisors and to be more productive in terms of numbers of publications compared with those with the least oversight and training." Davis, G. (May-June 2005). *Doctors without orders: Highlights of the Sigma Xi postdoc survey.* Special supplement to the *American Scientist.*

Provide Job Search Guidance and Support

Institutions and training programs should provide job search guidance and support to postdocs who plan to enter the private sector as well as those seeking academic positions. In the current apprenticeship model of biomedical training, postdocs who are searching for tenure-track positions within academia generally look to their PIs for job search assistance. PIs are able to help postdocs network, alert them to faculty job openings, assist with the preparation of application materials, and provide guidance during the interview process. Because most PIs have not experienced the job search process in the private sector, they do not have the expertise to provide the same degree of guidance to postdocs undertaking a job search in the private sector. Institutions and training programs must fill in this gap. Institutions and training programs can provide job search guidance by providing seminars on job search skills relevant to all career paths, offering one-on-one counseling with trained career services staff, or working with alumni or private sector companies to provide postdocs with additional mentors in the private sector.

(Question 11) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

Provide Training Specific to the Entrepreneur Career Path

As mentioned above, postdocs rarely receive training in general business concepts and soft skills. Such training is crucial if postdocs are to become successful entrepreneurs; they need business training in additional topics such as technology transfer, drug development, developing business models, and basic finance and accounting, as well as soft skills. Government, academia, and the private sector should work together to provide such training. Again, the NIH should allow release time for postdocs funded through its research grants to take advantage of such training. These seminars and courses should also be allowable training for postdocs funded through institutional (T32) and individual (F32) training grants.

Increase the Opportunities for Independence

While the postdoctoral experience is currently viewed as a training period in preparation for becoming an independent scientist, the current system does not promote exploration of independent ideas because the biomedical postdoc must most often focus on the research for which his/her PI has funding. To encourage entrepreneurship in the postdoc population, postdocs should be encouraged to develop their own independent, innovative ideas. **The NIH and other federal funding agencies should therefore consider a gradual increase in the number of postdocs funded by training or career grants.** This will increase the ratio of postdoctoral scholars funded by training grants to those funded by research grants, encouraging greater independence in postdocs. The NPA recommends increasing the number of postdocs funded by training or career grants from 6,800+ to 8,500+ over the next ten years, changing the ratio from a little of ¼ to approximately 1/3. We have only one caveat to this recommendation: that the entry-level stipend is $45,000.

Establish Intellectual Property Rights Conducive to Pursuit of Entrepreneurship

Intellectual property rights are often not available to postdocs. The research that they conduct usually becomes the property of the institution and/or PI. Unfortunately, the assignment of these rights are rarely well articulated to postdocs, who most likely did not negotiate with the PI regarding ownership of

data and publication rights and then are surprised to find that the PI/university controls the postdoc's data and use of that data. **Institutions and funding agencies should clearly articulate the intellectual property rights of postdocs and, as appropriate, allow postdocs the opportunity to participate in entrepreneurial activity based on the postdoc's research, whether initiated by the PI or initiated by the postdoc in collaboration with the PI.**

Thank you for your consideration.

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MARYLAND
Department of Business & Economic Development

Martin O'Malley Governor
Anthony G. Brown Lt. Governor
Christian S. Johansson Secretary
Dominick E. Murray Deputy Secretary

MEMORANDUM

TO: Dr. Michael Stebbins
Assistant Director for Biotechnology
Office of Science and Technology Policy
Executive Office of the President

FROM: Sally Kenyon Grant
Federal Policy Coordinator
DBED

CC: Dr. Judy Britz
Executive Director
Maryland Biotechnology Center

Dr. Charles Montague
Manager
Maryland Biotechnology Center

Rhonda J. Ray
Director of Policy and Government Affairs
DBED

DATE: December 6, 2011

SUBJECT: RFI: Building a 21st Century Bioeconomy
The White House - Office of Science and Technology Policy

To follow is our RFI: Building a 21st Century.

Building a 21st Century Bioeconomy

I. Introduction

On September 16, the President announced the development of a National Bioeconomy Blueprint (National Bioeconomy Blueprint), to be completed by January, 2012. The Blueprint will detail a new, Administration-wide effort to harness biological research innovations to address national challenges in health, food, energy, and the environment while growing the economy. The Office of Science and Technology Policy released a Request for Information on October 7, 2011(Request for Information), to solicit input to inform the development of the Blueprint. Tom Kalil, Deputy Director for Policy for the Office of Science and Technology Policy in the Executive Office of the President is directing the RFI.

The Maryland Biotechnology Center (MBC) is contributing to this RFI in the areas of "lab to market" by supporting and providing examples of:

- Promoting Commercialization and Entrepreneurship,
- Research and Development, and
- Workforce Development.

From the RFI and in response to the Administration's interest to learn further about steps to take to get science from lab to market, we are addressing seven points from the RFI and providing examples of programs in Maryland.

II. Outline

The seven areas that we will address in this paper include:

- RFI Outline No. (5) (We are combining 5 & 11)

  (5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

- RFI Outline No. (6)

  (6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs 2 would help accelerate commercialization of federally-funded bioeconomy-related research?

- RFI Outline No. (8)

  (8) What are the challenges associated with existing private-sector models (e.g.venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges? *Workforce development:* Investment in education and training is essential to creating a technically-skilled 21st century American bioeconomy workforce.

- RFI Outline No. 9

(9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

- RFI Outline No. 10

(10) What roles should community colleges play in training the bioeconomy workforce of the future?

- RFI Outline No. 11 (We are combining 5 and 11)

(11) What role should the private sector play in training future bioeconomy scientists and engineers?

- RFI Outline No. 12

(12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

III. Barriers Preventing Lab to Market
Federal Agency Support
Private Sector Training Opportunities

In the outline below, the Maryland Biotechnology Center will provide examples of initiatives that support lab to market programs in the State of Maryland. We will cite specific programs and leaders who have experience in research innovation initiatives that can be associated with high skill jobs.

- RFI Outline No. (5) Combined with RFI Outline No. 11

(5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

(11) What role should the private sector play in training future bioeconomy scientists and engineers?

Examples: The BioMaryland Alliance
The Maryland Industrial Partnerships (MIPS)
NIH Intramural Launch Program – For Post-Doctoral Fellows

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The Maryland Industrial Partnerships (MIPS)

The BioMaryland Alliance

The BioMaryland Alliance is a 501(c) 6 organization of business and community leaders created to facilitate Maryland companies working with the cluster of federal life sciences facilities located in Maryland ("facilities"), in particular the 27 Institutes and Centers that comprise the National Institutes of Health. The BioMaryland Alliance works to increase technology transfer and translational research opportunities at these facilities for Maryland companies by:

1) Facilitating communication and understanding with Maryland business leaders; and local, federal and state officials.

2) Promoting and supporting Maryland companies as they engage these facilities in business enterprise through contract relationships, collaborations, clinical trials, public-private partnerships, commercialization of technology, joint ventures and other activities; and

3) facilitating the transfer of technology and translational research activities at these facilities by increasing interactions with the business community and assisting in the development of policies which enable these activities to result in business growth for companies in Maryland.

The Maryland Industrial Partnerships (MIPS):

Concept:
Establish a NIST-based federal program based on the well-proven Maryland Industrial Partnerships program that effectively promotes commercialization of American innovations from US universities into US industry. By capitalizing on the base of research innovation in US universities, American companies can enhance their competitiveness and remain dominant providers of technology-based products.

Background:
A successful new economy relies heavily on intellectual capital and new technological innovations. Leveraging university assets to streamline product development and spur economic development makes sense, and fits into the NIST-MEP Next Generation Strategy to help manufacturers develop new products and new markets for US-made goods.

Why MIPS?
The Maryland Industrial Partnerships (MIPS) is a proven model for academic-industrial collaborations. MIPS has a 23-year history of successfully enhancing early stage technology commercialization. MIPS was recognized in March 2005 by the US Small Business Administration's Office of Advocacy as a best practices program in technology transfer in the US. The MIPS program could be broadly applicable in other US states in order to enhance technological competitiveness. There are fewer than five similar programs in existence now.

How does MIPS Work?
MIPS and Maryland companies jointly fund product development projects at the University of Maryland which must directly benefit the commercialization goals of the company. MIPS-supported products have achieved sales in excess of $21 Billion. MIPS often plays a critical role in proof of concept or prototype projects crucial to successful product commercialization. This is particularly true for start-up and newly emerging companies. The ideal situation occurs when innovations are carried directly to market by companies working hand in hand with university innovators.

What kind of technology can be developed?
The MIPS program can effectively work in a wide range of technologies including: biotech/life sciences, information technology, homeland security, nanotechnology, information security, telecommunications, clean energy/sustainability, environmental, optical and chemical technologies, etc.

How can MIPS be applied elsewhere?
Matched by state funds, federal funds could establish MIPS-like programs in any state that has an active research university system. By creating successful university-company linkages, states can compete more effectively in the new global economy. Federal funds would be matched not only by state funds, but also by corporate funds from participating companies. MIPS processes (application process, guidelines, contracts, evaluations) are well established (www.mipstrack.umd.edu) and could be applied immediately to other new programs.

What would this do for Maryland?
Maryland would become known as a leading state for innovation. With Maryland's history and track record of research and development (with more than $14 Billion in federal funds spent in Maryland alone on R&D), Maryland is uniquely positioned to be the leader in technology innovation programs. The missing piece has always been the ability to translate basic research into useful new products. Applying the award-winning MIPS model on a federal level establishes Maryland as a catalyst for US innovation.

What would this do for the US?
This new program would establish a smooth path for academic-industrial partnering throughout the US and help states compete in the global marketplace. The value of such a program may fundamentally change the way innovation proceeds to market. As the US has effectively invested in research, it must also invest in the ability to translate that basic work into products in the global marketplace. This would ensure the continued competitiveness of the US in the world.

NIH Intramural Launch Program – For Post-Doctoral Fellows

• At the orientation of new NIH fellows the Launch Program is presented as a viable career option.

• If interested, a post-doc begins entrepreneurship and business training during their fellowship using resources available in the Montgomery or Frederick County bio-incubator facilities. In parallel they begin discussing commercialization possibilities with their principal investigator (PI).

• When ready, the fellow licenses intellectual property from the NIH to form a new company or nonprofit entity, collaborating with their NIH PI in a seamless partnership that builds upon their subject matter expertise and the unique environment of the intramural research program.

• The NIH PI uses an amended IRTA mechanism to provide laboratory space, research funds, and a salary stipend to support the career development of their fellow; serving as a collaborator, mentor, and 'skin-in-the-game' vicarious entrepreneur to co-commercialize the science.

• Based on background and interest, the NIH PI may play a significant role in advising the fellow on commercialization activities, or may focus only on the scientific aspect and leave the business guidance to other mentors available within the Launch Program.

• The fellow shifts his or her emphasis to include both inventive- and discovery-based science to further the goals of the new entity.

• The fellow and PI engage in an extended and synergistic R&D partnership at NIH, with an understanding that some biotechnology efforts will take many years to complete.

• The fellow accesses federal, state, country, and private resources to raise funds to support the entity, and when ready opens a manufacturing center in a county bio-incubator or local facility.

• The partnership is renewable based on regular external reviews of progress, using both academic (scientific publication) and commercialization (product development) milestones.

• Special emphasis is placed on encouraging, starting, mentoring, advising, and supporting women- and minority-owned entities, including use of government set-aside programs.

• Exit strategy – even with the advantages of an NIH partnership, many entities will fail. In that circumstance, a terminal year of support will be provided and the post-doc will be considered to have formally completed a second NIH fellowship with an emphasis on entrepreneurial training.

• Metrics of Launch Program Success:

1. Provide exciting career option for a subset of NIH fellows – new opportunity for early scientific independence outside the traditional academic system.

2. Increase utilization of NIH intramural inventions and discoveries for public good.

3. Create women- and minority-owned businesses and research institutions.

4. Royalty- and equity-based payments to NIH to support additional basic research.

5. Economic value to local, state, and national economies.

6. Business innovation, e.g., two NIH post-docs join forces to spin out a non-profit entity using a scientific crowd sourcing business model that nobody thought of before...x 1000.

II. SBIR and STTR Programs to Accelerate Commercialization of Federally-Funded Bioeconomy Related Research

- RFI Outline No. (6)

(6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs 2 would help accelerate commercialization of federally-funded bioeconomy-related research?

Example: **TEDCO**

State Partner: **Rob Rosenbaum**
rrosenbaum@marylandtedco.org
410-740-9442

TEDCO

The Maryland Technology Development Corporation (TEDCO), an independent entity, was established by the Maryland General Assembly in 1998 to facilitate the transfer and commercialization of technology from Maryland's research universities and federal labs into the marketplace and to assist in the creation and growth of technology-based businesses in all regions of the State.

In 2008, for the fifth consecutive year, *Entrepreneur magazine* ranked TEDCO #1 as the most active investor in seed/early-stage companies in the nation (the magazine has not produced a report since 2008).

TEDCO's mission is to:

- *Support* transferring to the private sector and commercializing the results and products of scientific research and development conducted by colleges and universities and the federal laboratories in the State of Maryland.
- *Assist* in the commercialization of technology developed in the private sector.
- *Foster* the commercialization of research and development to create and sustain businesses throughout all regions of the State.
- *Promote* entrepreneurship and the creation of jobs in technology-related industry by establishing and supporting effective business incubators throughout the State that provide adequate physical space and programs to increase or accelerate business success in the field of technology.

TEDCO's role is to be Maryland's leading source of funding for seed capital and entrepreneurial business assistance for the development, transfer and commercialization of technology. To date, TEDCO's portfolio totals 244 companies.

As a government intermediary, TEDCO has done the following programs:

- TEDCO Hosts Small Business Innovation Research Conference

  TEDCO's conference aims to provide Maryland's Small and Minority Businesses with the necessary tools to master the complexities of the SBIR application process, and understand the intricacies of the selection process while tapping into the minds of the selectors.

Panelists include:

• experts from federal agencies
• qualified speakers on SBIR funding
• specialists in the venture capital community
• industry leaders skilled at taking small businesses from product development to commercialization

- Maryland Technology Transfer and Commercialization Fund (MTTCF): MTTCF, TEDCO's signature program, provides up to $75,000 as a reimbursable award for initiation of technology transfer projects that involve collaboration between a Maryland company and any federal laboratory or academic research institution in Maryland as well as a tenant in one of Maryland's technology incubators. Funds are to be used to defray direct costs of further developing early-stage technology. TEDCO has made investments in 169 MTTCF companies. With TEDCO's support these companies have collectively raised downstream funding from venture and angel investors, government grants (e.g. NIH, SBIR), private placements, product sales, etc., for a leverage of the State's investments through TEDCO of over $42 to $1.

- University Technology Development Fund (UTDF): The UTDF provides up to $50,000 for proof-of-concept studies or patent extension research on Maryland university-owned technologies to demonstrate their ability to meet identified market needs. The objective is to make the technologies more attractive to licensees preferably based in Maryland.

- TechStart Program (TSP): TSP provides up to $15,000 to further evaluate the feasibility of a technology from a Maryland university or federal lab to be the basis of a startup company. The feasibility team must include the principal investigator, entrepreneur, and tech transfer manager. Funds are to be used for tasks critical to determining the viability of a new company formed around the spin-out technology.

- Rural Business Innovation Initiative (RBI2): The RBI2 program supports technology-based companies in rural Maryland. The program provides intensive business and technical assistance to help companies advance to the next level. Companies may receive a maximum of $7,500 of assistance provided by industry experts.

- Maryland Stem Cell Research Fund (MSCRF): MSCRF provides a variety of grant programs for human stem cell research in the State of Maryland, including: Investigator-Initiated Grants, Exploratory Grants, and Post-Doctoral Fellowships. Maryland-based organizations of all types are eligible for the grants. Such organizations include public and private, for-profit and nonprofit, universities, colleges, research institutes, companies, medical centers and others. Funding of $55,000 to $500,000 a year is available. For more information please go to www.mscrf.org.

- Joint Technology Transfer Initiative (JTTI): TEDCO has contracted with the Department of Homeland Security (DHS) and the U.S. Army Medical Research and Materiel Command (USAMRMC) to facilitate transfer of technology. Funding up to $75,000 is available to company can show how the proposed technology will meet the needs of DHS and/or USAMRMC (Spin-In) and/or the commercialization of DHS or USAMRMC technologies (Spin-Out).

- Working Capital Loan Fund (WCLF): WCLF is designed to provide loans to incubation-stage, technology-related companies in Maryland. The maximum loan is $50,000, with low interest rates and flexible terms, and includes a quick turn-around from application to a decision. Funds can be used to assist a company with expansion, market entry, staffing or other working capital needs.

INCUBATOR INITIATIVES

- Incubator Development Fund: This is a funding program designed to support the capital needs of developing a new incubator facility or renovating an existing facility. The funding leverages other private and public investment.

- Incubator Feasibility Study Grant Program: The Incubator Feasibility Study Grant Program is designed to assist higher education institutions and local economic development organizations in creating and expanding technology business incubators. The grant funds are used to hire a consultant to complete a feasibility study for a technology incubator. TEDCO provides matching grant dollars up to $30,000 per study.

- Intensive Business Assistance Program: This program promotes the growth of technology companies in the State of Maryland through support of business incubators. Each of the 19 technology incubators receives an annual grant, based on a Scope of Work, to provide targeted business assistance services to their tenants and affiliates.

TEDCO Program – NASA Technology Opportunities

TEDCO can help identify NASA-sponsored research, technology, technical expertise and R&D capabilities that match the needs and interests of your business. TEDCO assists Maryland businesses to improve their competitiveness by providing free technical assistance and information to help resolve specific technical questions or needs that can be addressed within a limited amount of time. This is routinely done on a confidential basis. Also, TEDCO funding programs can help you develop NASA technology.

Currently Featured NASA Technologies
For the convenience of Maryland companies TEDCO has listed some of the promising NASA technologies here:

- Goddard Space Flight Center

TEDCO can help you with questions regarding a NASA technology match, establishing technology agreements with NASA, patenting products and intellectual property, working with NASA scientists to commercialize new products, and measuring program success. NASA is deeply committed to spreading the unique knowledge that flows from its aeronautics and space research to businesses. Numerous technologies originally developed for NASA missions have wide commercial application and are now available for license.

TEDCO provides Maryland companies with information about these “technology opportunities” and how to pursue them within NASA. NASA is also seeking industrial partners to pursue joint research and development projects that have potential application to both NASA missions and the commercial market. TEDCO serves as a point of contact for businesses seeking information about

NASA technologies. TEDCO will work with you to understand your specific opportunity, question, or need. We will then provide assistance through our own expertise, the knowledge base of NASA, and other partners within the TEDCO family. After providing the assistance, we may send you a brief evaluation survey to determine your satisfaction and the economic impact of our assistance.

TEDCO Program Links to Federal Labs

Federal Labs Consortium

NAVY

- Pax River
- Carderock
- Naval Medical Research Center
- Indian Head
- NAVAIR

NIST - National Institute of Standards and Technology

NASA

- Goddard Space Flight Center

NSA - National Security Agency

NIH - National Institute of Heath

- Seeking an NIH Grant?
- NCI
- NCI-Frederick

ARMY

- Army Alliance for Technology
- Aberdeen Proving Ground
- Science & Technology Board at Aberdeen
- Center for Health Promotion & Preventive Medicine
- Army Research Lab
- Fort Detrick

APL - Applied Physics Laboratory

ARS - Agricultural Research Service

- Beltsville Agriculture Research Center

III. Challenges for Financing Entrepreneurial Bioeconomy Firms

- RFI Outline No. (8)

  (8) What are the challenges associated with existing private-sector models (e.g.venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges? *Workforce development:* Investment in education and training is essential to creating a technically-skilled 21st century American bioeconomy workforce.

Example: **Greater Baltimore Committee (GBC)**

State Partner: **Lizbeth Pettengill,**
Vice President and Director of Membership
Greater Baltimore Committee (GBC)
111 South Calvert Street, Suite 1700
Baltimore, MD 21202

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lisbethp@gbc.org

The Greater Baltimore Committee (GBC) is a regional, membership organization of more than 500 businesses, nonprofit organizations, and educational and civic institutions. Members are located in Baltimore City and Anne Arundel, Baltimore, Carroll, Harford and Howard counties.

The GBC's mission is to improve the region's business climate by organizing its corporate and civic leadership to develop solutions to problems that affect the region's competitiveness.

GBC can work toward leveling the funding field between academia and commercial companies. Far too great a percentage of federal funding goes to universities with a focus on basic research, grant procurement and publication. GBC, in the private sector, would like to see major research universities held accountable for how these funds are spent and what practical outcome(s) they achieved. GBC would like to see far more federal funds in bioscience directed toward small and emerging company funding. Finally, GBC would like to see a significant increase in the percentage of funds currently allocated for SBIRs for small companies.

IV. Professional Training Programs to Prepare Scientists for Private-Sector Bioeconomy Jobs

- RFI Outline No. 9

  (9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Examples: **Johns Hopkins University**

1.) **Center for Biotechnology Education at Johns Hopkins**

2.) **Masters in Biotechnology Enterprise and Entrepreneurship**

3.) **Certificate in Biotechnology Enterprise**

4.) **Joint MS Biotechnology/MBA**

5.) **Johns Hopkins University Carey Business School INNOVATE Technology Commercialization Program**

Professional Science Masters (PSM) at UMBC

Biological Sciences Department Graduate Programs at UMBC

State Partners:

Lynn Johnson Langer, PhD, MBA
Johns Hopkins University
Director, Enterprise and Regulatory Affairs Programs
Center for Biotechnology Education
9601 Medical Center Drive
Gilchrist Hall, Room 104
Rockville, MD 20850
301-294-7063

www.biotechnology.jhu.edu

Johns Hopkins University

1.) **Center for Biotechnology Education at Johns Hopkins**

2.) **Masters in Biotechnology Enterprise and Entrepreneurship**

3.) **Certificate in Biotechnology Enterprise**

4.) **Joint MS Biotechnology/MBA**

Professor Antonio R. Moreira
Vice Provost for Academic Affairs
University of Maryland, Baltimore County
moreira@umbc.edu

Professional Science Masters (PSM) at UMBC

Biological Sciences Department Graduate Programs at UMBC

Johns Hopkins University

1.) LANGUAGE REGARDING CENTER FOR BIOTECHNOLOGY EDUCATION

About the Center for Biotechnology Education

The Johns Hopkins University Zanvyl Krieger School of Arts and Sciences created the Center for Biotechnology Education to engage diverse audiences in the world of biotechnology and to prepare the leaders of today, tomorrow, and the next generation for the challenges of the 21st century. By expanding the scope of biotechnology education, the Center for Biotechnology Education is building a pipeline of students and professionals prepared to achieve success in K-12 education, graduate school, and the work environment in the fields of biotechnology, bioinformatics, bioscience regulatory affairs, and bioscience business and leadership.

The Center's mission is to expand the reach of biotechnology education through three channels:

- **Graduate Education -** Our graduate programs are designed for working professionals – delivering the rigorous and practical curriculum they need to advance their careers or academic ambitions. Johns Hopkins' Advanced Biotechnology Studies (ABS) Program is rooted in the multidisciplinary skills of basic research, drug discovery technologies, bioinformatics, regulatory affairs, and product commercialization. The program offers four master's degrees, graduate fellowships, and certificates.
- **Youth Programs –** Inspiring the next generation to explore the world of biotechnology is an important objective of the Center. We developed several hands-on programs for children in elementary, middle and high school that introduce them to this exciting field.
- **Professional Development –** Orchestrating partnerships with industry and government organizations to provide community outreach, professional development, educational opportunities, workshops, research symposia, and lecture series for academia, industry, and the general public.

Our goals are to increase public awareness and understanding of biotechnology, to inform educators of the resources and programs available locally and nationally, to become a resource center for biotechnology information, to coordinate training workshops for students and professionals, and to support biotechnology training and education locally, nationally, and internationally.

2.) LANGUAGE REGARDING MASTERS IN BIOTECHNOLOGY ENTERPRISE AND ENTREPRENEURSHIP

Masters in Biotechnology Enterprise and Entrepreneurship

For a biotechnology enterprise to be successful, it requires trained professionals who understand science and who are also skilled in the complexities of biotechnology commercialization. This exciting new program brings together a strong science foundation with biotechnology enterprise and entrepreneurship.

About the Program

This new master's program is intended for biotechnology professionals who seek a career beyond the laboratory either within an existing biotechnology group or organization or for those who seek to start a new biotechnology enterprise. The curriculum is designed to prepare the next generation of interdisciplinary professionals to address the enterprise and regulatory challenges organizations face in the biotechnology industry.

Students will complete 10 graduate courses, including a final practicum course to gain real-world experience. Students may choose three electives across a broad range of science, enterprise and regulatory courses, (no more than one elective may be a business course) or they may choose a concentration in Bioscience Communications or Legal/Regulatory Affairs.

Courses are offered at the Homewood campus, the Montgomery County Campus, as well as online. The entire degree can be completed online or a combination of online and on-site.

3.) LANGUAGE REGARDING CERTIFICATE IN BIOTECHNOLOGY ENTERPRISE

Certificate in Biotechnology Enterprise

Merging science and business is at the center of biotechnology. Students who want to become part of the development and commercialization of science must first understand the running of a biotechnology organization. To acquire this experience and knowledge, students can earn a Certificate in Biotechnology Enterprise. This certificate offers the opportunity to learn critical aspects including how to create a new enterprise, finance, marketing, and other areas of commercialization. This certificate is ideal for students planning to engage in the enterprise of biotechnology beyond the science. Applicants should have an undergraduate degree preferably in the life sciences with a grade point average of 3.0 on a 4.0 scale.

Certificate requirements consist of five courses. Students who successfully complete the certificate and subsequently decide to seek admission to the master's degree program in biotechnology or bioscience regulatory affairs will receive credit for three of the courses taken in the certificate toward the master's degree. Conversely, students who complete their master’s degree first, may count 3 of their enterprise courses toward the certificate.

4.) LANGUAGE REGARDING JOINT MS BIOTECHNOLOGY/MBA

Master of Science in Biotechnology/MBA

A joint offering of the Zanvyl Krieger School of Arts and Sciences and the Carey Business School

In today’s aggressive biotechnology business environment, there is an acute need for leaders who understand both the science and business of biotechnology. Johns Hopkins University offers one of the nation’s first joint graduate degree programs in biotechnology and business. Graduates earn two Johns Hopkins degrees. The program allows students to master areas such as biochemistry, biostatistics, and bioinformatics while developing critical business skills in areas such as accounting, finance, negotiation, and regulatory and legal matters.

FLEXIBILITY
Designed for working adults, the Master of Science in Biotechnology / MBA graduate degree program offers a part-time program of study. Courses are taught during evenings or weekends at the university's Montgomery County Campus in Rockville, MD.

STRENGTHS
The joint degree program allows students to earn two advanced degrees in less time than it takes to earn them separately. Students complete 10 courses for the MS in Biotechnology and 14 for the MBA. Students follow a curriculum sequence allowing them to complete both degrees in three years.

As one of the largest biotechnology and business programs, and ideally situated both in the Shady Grove Life Sciences Center and near federal research and regulatory agencies, the program capitalizes on the strengths of leading experts, Johns Hopkins academics, and a diverse student body.

5.) JOHNS HOPKINS UNIVERSITY CAREY BUSINESS SCHOOL INNOVATE TECHNOLOGY COMMERCIALIZATION PROGRAM – NON-CREDIT

Starting in February 2010, the Carey Business School will offer a technology commercialization program, titled Innovate!, at the Johns Hopkins University Montgomery County Campus.

Innovate!, which is funded by a National Science Foundation grant to the Johns Hopkins University and the University of Maryland, Baltimore County, is a 12-month program led by successful serial entrepreneurs that will take a class of 15 business professionals and 15 postdocs through evaluation of a technology's commercial viability, preparation of a business case based on the technology, and launch of the business. The businesses will be based on technology from NIH, Johns Hopkins University, the University System of Maryland, and other research institutions and federal agencies.

"The Innovate! program is perfect for professionals who have thought about starting their own technology company and are looking for a supportive, structured environment to help make it happen," said Yash Gupta, Dean, Johns Hopkins Carey Business School.

"We're extremely excited to have the Innovate! program on our campus because it fits so well with the county's economic development goals," said Elaine Amir, Executive Director, Johns Hopkins Montgomery County. "The county recently released its Biosciences Task Force report, and one of the report's five key objectives was to 'enhance the environment for entrepreneurship and the creation of new life sciences companies.' It's great that Johns Hopkins can help advance that goal."

The Innovate! program is based on the highly successful ACTiVATE® program at the University of Maryland, Baltimore County, which has led to the formation of more than 25 companies since its inception in 2005.

Partners for the Innovate! program include Rockville Economic Development, the Montgomery County Department of Economic Development, and the National Institutes of Health.

Professional Science Masters (PSM) at UMBC

The Professional Science Master's (PSM) degree is an innovative two-year graduate degree designed to allow students to pursue advanced training and excel in science while simultaneously developing highly-valued business skills. PSM programs prepare students for science careers in business,

government, or nonprofit organizations, where workforce needs are increasing. Programs are characterized by "science-plus," combining rigorous study in science or mathematics with skills-based coursework in management, policy, or law. PSM programs emphasize writing and communication skills, and most require a final project or team experience, as well as a "real-world" internship in a business or public sector enterprise.

The PSM programs now recruiting are of three kinds:

- Those that deepen a student's knowledge beyond what can be learned in a four-year course of study, but stay within a disciplinary domain;
- Those that fuse scientific fields at a level of depth and complexity hard for undergraduates to achieve; in many cases, the fusion may be with computer or information sciences; and
- Those that integrate study in the natural sciences and mathematics with knowledge and training in management, law, or other professional domains.

Programs are developed in concert with industry and are designed to dovetail into present and future professional career opportunities. Graduates are equipped to manage the breakthroughs that are created by the research teams. They can interact between researchers and managers, especially in the marketing, finance, and legal departments.

The PSM began in 1997 with a series of grants from the Alfred P. Sloan Foundation to selected research universities. (Background on the PSM initiative.)

PSM Reports and Statistics

Enrollment and Degrees in Professional Science Master's (PSM) Programs: 2010

The *2010 Professional Science Master's Enrollment and Degrees Survey* is an annual survey of enrollment and degrees in Professional Science Master's (PSM) programs. Previous PSM enrollment and degrees surveys were conducted for academic years 2008 and 2009 by NPSMA, the National Professional Science Master's Association. The revamped 2010 survey was carried out by CGS with a grant from the Alfred P. Sloan Foundation. It collected data regarding applications, first-time enrollment, total enrollment, and degrees awarded.

Outcomes for PSM Alumni: 2010/11

The *2011 Professional Science Master's (PSM) Student Outcomes Survey* was conducted by the Council of Graduate Schools with a grant from the Alfred P. Sloan Foundation. The survey was designed to capture initial hiring outcomes of PSM graduates and follow them for up to five years after graduation. The design was based upon a review of more than 40 outcomes-related data collection efforts from more than 30 governmental agencies, non-profit organizations, and educational institutions. A draft version of the questionnaire was reviewed by numerous individuals affiliated with the PSM initiative, including members of the Board of Directors of the National Professional Science Master's Association (NPSMA) and members of the Council of Graduate Schools PSM Advisory Board.

Companies That Have Hired PSM Graduates

Applied Physics and Health Physics

Argonne National Lab
Boeing
Entergy
Geisinger Health System
Illinois Department of Nuclear Safety
Lockheed Martin, thermo-analysis of small satellites
Mayo Clinic
Raytheon, various
Spectrum Astro
Thomas Jefferson Accelerator

Environmental

Alameda County Water District, GIS water analyst
Cold Regions Research and Engineering Laboratory
Conservation Biology Institute
Institute of Pollution Control, Tech. Development
Minerals Management Service, Leasing & Environment Mapping and Automation
MODIS Rapid Response Team, NASA
Natural Resources Conservation Service, cartographic technician
Patrick Engineering, GIS Analyst
STS Consultants Ltd in Wisconsin; graduate is doing GIS analysis
U.S. Department of Natural Resources, Storm Water Manager
U.S. Environmental Protection Agency
Vestra Inc. GIS Analyst

Financial, Industrial Mathematics, Statistics

American Automobile Assoc.
Chevron
Digital Credit Co.
First Federal Bank
G.E. Capital
Guidant
Lockheed-Martin
Minitab Inc.
Putnam Investments
Roche Diagnostics
Southeastern Michigan Council of Government
U.S. Department of Agriculture
Watson-Wyatt

<u>Companies That Have Hired PSM Graduates and Supported PSM Students</u>

Applied Biosciences/Biotech

ActivX Bioscience Inc.
Affymetrix
Allergan

Alltech Inc.
Amgen
Avery Point Marine Sciences
Bear Stearns
BIOCOM
Boehringer-Ingelheim
Catalyst Pharmaceuticals
Ceres Inc.
Cisco Systems
CombinatoRx Inc.
Department of Homeland Security
Eli Lilly
Florida Department of Law Enforcement
Genomatica
Glaxo SmithKline
Health Sciences Inc.
Informax
Johnson & Johnson
Kyroten
Life Sciences, Inc.
Neurogen
Northrup Grumman
Novartis
Performant
Pfizer Labs
Pregrine Pharmaceuticals
Purdue Pharma
Quintiles
Roche Molecular Systems
Sanger Institute
Texas Department of Public Safety
The Institute for Human Genome Therapy
Thermo -Electron
3-Dimension Pharmaceuticals (Johnson & Johnson)
Toronto Children's Hospital
UCLA Office of Intellectual Property
United Devices
Zuyder Pharmaceuticals

Applied Physics and Health Physics

Mallinckrodt Inc.
State of Michigan
U.S. Army
Wake Forest Hospital

Financial Math, Industrial Math, Applied Statistics

American Automobile Association
Blue Cross Blue Shield

Boeing (St. Louis)
Census Bureau
Deloitte Touche Tohmatsu
Essayons Consulting (Tacoma)
Hershey Medical Center
Jackson Life
Johns Hopkins Quality and Safety Research Group
Lockheed-Martin
Keykert USA
Progress Energy
Watson-Wyatt

Materials and Chemical Synthesis

Henkel Technologies
Northview Laboratories

Other

Control Delta Institute (Env.)
Convers (Carlsbad CA)Dallas Zoo
EarthIT (Madison WI)
General Dynamics Network System
NASA
Shriner's Children's Hospital
South Carolina Department of Health and Environmental
SYSTRAN

Employer Testimonials

"We found … [his] level of productivity was at a much higher level, equivalent to that of a senior scientist. In fact his ability to work unsupervised allowed us to send him on international assignments that required him to be, self sufficient, scientifically competent and knowledgeable about proper business etiquette. In addition, the University facilitated the process to the point where things were taken care of in a swift and effortless manor."

Enrico Picozza
President and CEO of HTS Biosystems and Entrepreneur
Comments on a University of Connecticut, Applied Genomics Intern

"Professional science masters (PSM) degree programs represent a significant revolution in graduate science education. They serve students, universities and employers in an almost ideal way -- business and industrial advisors help university faculty and staff prepare students for careers where scientific and mathematical depth, and personal development are in high demand. Typically, graduates earn "knowledge worker" careers that are stimulating and well-paid from the start and can lead to considerable advancement. I wish these programs existed when I was completing my education!"

"I work at the Ford Motor Company where teams of students from MSU's Industrial Mathematics PSM have done well with four projects Ford has sponsored. We also benefited from an internship

and just recently (in a time when the Ford staffs are shrinking) hired our first graduate from this PSM program. This PSM has the attention of several Ford executives -- we look forward to more involvement."

Phil Tuchinsky
Technical Expert, System Analytics and Environmental Sciences Dept.
Ford Research & Advanced Engineering
Ford Motor Company

"PSM programs graduate individuals with the technical skills of a regular master's graduate and added business acumen. Graduates have the marketing savvy and excellent written and verbal communication skills necessary to survive in business-centric technical positions, e.g. sales engineer, project manager, lead engineer, CTO, CEO, and other executive positions."

Kathleen Perkins
CEO, Breault Research
Tucson, Arizona

"Students in the Professional Master's Degree Program in Applied Biosciences should find advancement prospects significantly enhanced in the biotechnology industry, particularly relative to more traditional master's degreed students."

David Robinson
Chairman, President, and CEO, Ligand Pharmaceuticals, Inc.
Chairman of the Board and Director, Biotechnology Industry Organization

"The ... Professional Master's Degree Program serves a great and constantly growing need in industry to produce students who are technically savvy and have a high degree of knowledge in the applied sciences, as well as a comprehension of the fundamentals of business and professionalism. Industry needs employees who not only understand the technical nature of their projects, but the business and legal aspects as well, and are able to communicate their mission to broad audiences. Students in this unique program learn just that. The Professional Master's Degree Program produces students who understand science and business and the inherent connection between the two disciplines in industry. The success of science professionals is based on individuals who understand these connections, and the ... Professional Master's Degree Program gives its graduates the skills to excel in their careers."

Lois A. Dimpfel
Vice President, Global Services (Retired)
IBM Corporation

"Genomics is becoming an essential science for medical discovery. Genomics is in its infancy and needs scientists that are eager to explore new, evolving technologies. Graduates of the ... Professional Masters program have the skills, experience, and knowledge for successful, fulfilling careers in genomics."

Pamela M. Carroll, Ph.D.
Senior Research Investigator
Applied Genomics Pharmaceutical Research Institute
Bristol-Myers Squibb Company

"Individuals with an educational background in these interdisciplinary areas are very few in number. [The] idea of combining a rare and highly demanded technical education with a modest exposure to training in business will produce students who are truly unique, and these students will be highly recruited by industry."

Ken Smith
Co-founder of Carbon Nanotechnologies, Inc.

"Environmental consulting companies seek to hire motivated individuals with a solid background in applying quantitative skills to solve and prevent environmental problems. In addition, as consultants, these individuals need to be able to communicate effectively and have a keen sense of management and business practices. Graduates from [the] Professional Master's Program in Environmental Analysis and Decision Making will possess these qualities and be a tremendous asset to us and others in our field."

Chuck Newell
Vice President
Groundwater Services, Inc.

"Students in the Professional Master's Program benefit from ... well-recognized academic resources enhanced with professional components that together foster the development of essential science, communication, and management skills. The Subsurface Geoscience track creates a rare breed of well-prepared professionals possessing the wide range of abilities necessary to devise innovative and pragmatic approaches to tackle difficult industry problems."

André Erlich
Chief Information Officer
Schlumberger Ltd.

UMBC Biological Sciences Department Graduate Programs

UMBC's Department of Biological Sciences is one of the university's largest academic departments, encompassing a wide breadth of research and teaching with foci in the following areas:

- Cell Biology
- Computational Biology
- Developmental Biology & Immunology
- Evolutionary Biology
- Molecular Biology & Genetics
- Neuroscience
- Plant Biology

With 27 tenured and tenure-track faculty members and seven instructors and lecturers, the department offers a full complement of baccalaureate and graduate programs leading to B.A., B.S., M.S., and Ph.D. degrees, which are recognized for their emphasis on research, scientific approach, faculty contact, and extensive lab offerings. These programs serve to train a broad spectrum of future biologists and researchers and to prepare students for graduate and professional schools.

UMBC's Department of Biological Sciences also sponsors a PSM program in biotechnology. The curriculum provides advanced instruction in the life sciences, along with coursework in regulatory

affairs, leadership, management, and financial management in a life science-oriented business. Eight active industry professionals are engaged as instructors to provide state-of-the-art learning experiences to the students.

The department also offers the M.S. in Applied Molecular Biology, started in 1983 as the first program of its kind in the country. During two semesters, the students learn the science underlying biotechnology by taking two lecture courses each semester. The hands-on methods of molecular biology are learn via two semesters of a 7-credit, 20 hr./wk. project-oriented lab course. The primary purpose of the program has been and is to train students to take middle level positions as research scientists in the biotechnology industry. Others, continue their education by joining Ph.D. programs, often at UMBC, or go to medical, dental and veterinary medicine schools. Several have gone to law school to become patent attorneys. And, some of the students accepted into medical school enter MD-Ph.D. programs.

V. Community College's Role in Training the Bioeconomy Workforce

- RFI Outline No. 10

  (10) What roles should community colleges play in training the bioeconomy workforce of the future?

Examples: **Chief Science Officer Program at Montgomery College, Maryland**
Biotechnology Program, Montgomery College

State Partners:

Steve Greenfield
Instructional Dean
Montgomery College
Business, Information Technology, & Safety
Workforce Development & Continuing Education
240-567-2583 -- office
240-567-1893 -- fax
301-512-9947 - mobile
steve.greenfield@montgomerycollege.edu
http://www.montgomerycollege.edu

Chief Science Officer Program at Montgomery College, Maryland

Dr. Collins Jones
Associate Professor
Montgomery College
Biotechnology Coordinator of Business
Tel: 240-567-1910
Collins.jones@montgomerycollege.edu

Biotechnology Program, Montgomery College

Chief Science Officer Program at Montgomery College, Maryland

The course will provide tools, knowledge, and skills needed to move up the career ladder from research into scientific management and leadership in the federal, academic, or commercial sectors. Send a signal to hiring managers that you are prepared for a scientific management career by adding this 36-hour course and certificate of completion to your resume.

The CSO Program at Montgomery College is designed for students, postdocs, and other technical professionals making the transition to business and industry and seeking preparation for leadership and management positions. It will show you the skills that are required, guide you in assessing your current skill levels, and provide the training to address your weaknesses to become not only competitive in landing an industry job, but successful in that job as well.

One of the most effective and unique features of this program is how the instructors relate "business" concepts to activities and behaviors commonly experienced by academic scientists. This approach helps students gain a deeper understanding of how their own experiences can strengthen their competitiveness for industry positions. The course also provides a self-assessment tool that introduces students to each of the 24 competencies, has them rank their own skill levels, and helps them develop "experience statements" from their own careers that support these rankings. A detailed report generated by the assessment tool then maps the student's capabilities to those that are critical to different kinds of jobs in different industries. The instructors will then show how to use this information to develop powerful targeted resumes and to prepare for effective interviews.

Jump Start Your Career!

- Individualized leadership assessment of your knowledge and skills
- Leadership Training
- Substantive topics: negotiation, project management, first-line supervision and finance, and a full set of elective offerings
- Individualized leadership inventory of knowledge and skills gained during the course
- Customized career plan for your career

A Focus on Core Concepts for CSOs

Success as a Chief Science Officer in industry is dependent upon appreciating and understanding five key management concepts. It is no longer just about the science, but how well you can utilize the scientific capital (in all its forms) at your disposal. The needed skill sets are the same regardless of whether you are coming from a physical sciences or life sciences background—it is really about interpersonal skills and fully appreciating the goals and functions of a business organization that will lead to long-term career success.

To ensure this, the CSO boot camp will focus on five “fundamental” topics—essential skills that no seasoned corporate scientific leader can be without! These key concepts are:

- Leadership Training—How can you be a successful “boss” on a personal level as well as an organizational level?
- Project Management—In industry it’s all about meeting the corporate deliverables on time and on budget. Can you deliver the goods?

- First-line Supervision—Successful companies get things done through teams, and interpersonal skills are the key to getting things done through people.
- Negotiation—The success of your company and your career will depend on how well you negotiate tasks and rewards. How prepared are you for this?
- Finance—A company is ultimately graded on its financial success rather than specific scientific accomplishments. Do you understand and appreciate it?

Introduction to a Variety of Electives

During the CSO boot camp, participants will also have the opportunity to attend introductory lectures in a variety of relevant areas that they choose. These include:

- Business Development for Scientists—as a scientist, learn how to take a practical hands-on approach to business plan development, venture capital and technology transactions.
- Marketing Strategies—See how science-based firms can use marketing to help reach their goals in technology development, product commercialization or other organizational needs.
- Law and Contracts in the Pursuit of Science—Explore how basic business, legal and regulatory concepts impact the work of scientific organizations and apply across the scientific landscape.
- Technology Transfer—Even the best scientists can no longer "do it alone," particularly in terms of commercialization. Learn the key concepts of accessing discoveries, collaborations and other resources at outside organizations, including university and federal labs.

Montgomery College—Workforce Development & Continuing Education (WD&CE) conducted exit interviews for each of the four scholarship students in an effort to thoroughly understand the impact of the course as well as the scholarship. Students also completed course evaluation forms which can be made available if FLC would like to review them.

Based on the exit interviews, the course had the intended outcomes, including having a significant impact on students' ability to enter into management and leadership careers and/or pursue successful career progression in the bio-tech industry. Scholarship students identified the following themes and competencies gained:

- Learned new aspects of leadership/management;
- Learned how to identify latent or already-existing leadership skills;
- Learned how to re-construct the resume based on leadership skills learned;
- Learned how businesses are designed and how they run;
- Learned the difference between leadership and management;
- Learned to be aware of the leadership in their current organizations;
- Learned self-awareness and how to identify gaps in personal leadership skills and how to address those gaps; and
- Learned how to enhance career development.

Steve Greenfield, Instructional Dean, Montgomery College-WDCE, and
Transcie Almonte, Acting Director, Montgomery College-WDCE Management Programs.

<u>Scholarship Recipients</u>

Diana Huestis: A post-doc for three and half years, (one at Kansas State University and now two and half here), Diana currently works at Laboratory of Malaria and Vector Research (LMVR), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH). The course helped her learn how to translate leadership/communications skills that have already been in practice into descriptions for CVs/resumes for job seeking and learning new aspects of leadership/management that she hadn't already learned in a classroom or thought much about. She already updated her CV to reflect what she learned in the course, and hope it will help with her ongoing job search.
Clarisa Buckner: A post-doc for two and half years and currently works at the National Institutes of Health, NIAID. CSO Module 1 was an eye-opening experience for her. In this module she learned about how to be a leader versus a manager. In defining the roles and distinguishing the two, she is now more aware of the players in her organization. She is also now aware of how businesses and organizations are designed and run. According to Clarisa, this class taught her proper etiquette in the workplace and she is now more in tune with what role she would like to play in an organization. Clarisa looks forward to Module 2 where she will learn more of the business terminology, as well as such topics as Project Management and Finance. She truly believe this course prepare scientists to enter industry because they are unaware of the business aspects and environment.
Khadija Ben-Aissa: A post-doc for six years and currently works at the NIH. The course helped him know how to leverage his qualifications as a scientist in academia to match qualifications needed to work in Industry. It also helped him identify gaps he can work on to successfully meet requirements to find a job in the Industry.
Heather Lucas: This is her fourth year as a post-doc and she is currently working at the National Institute on Aging, Baltimore, MD. The course helped her to gain a different perspective from what is typically available to a postdoctoral fellow or research scientist in a traditional laboratory setting. Throughout her career, she has taken on many leadership roles and the structure of the class has allowed her to put that into perspective, from creating a vision to developing a performance plan. By discussing the attributes that make a great leader within the class, she learned about herself and others in a way that will enhance her career development and benefit her long into the future. Furthermore, the opportunities to network within the class have helped her to shape her personal goals. After completion of the final module and as she progresses towards her future career, she looks forward to corresponding with Randy Ribaudo (Human Workflows) and receiving feedback from him. Heather feels this will be a valuable asset that she finds advantageous as she competes in a tough job market. Darlene Floyd (leadership instructor) was the highlight of this course!

Biotechnology Program, Montgomery College

The Biotechnology Program trains students for jobs in the biotech industry. Entry-level workers are involved in laboratory work such as:

- Cell culture and upstream processing
- Antibody production and isolation
- DNA isolation, PCR, RT-PCR and qPCR
- Toxicology or vaccine sterility testing
- Testing and developing diagnostic and therapeutic agents

Courses toward a degree or certificate are designed to prepare students for both academic achievement and successful employment in the biotechnology industry.

VI. Encouraging Successful Entrepreneurship

- RFI Outline No. 12

  (12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

Examples: **Maryland Technology Enterprise Institute (MTECH)**

State Partner: **Martha J. Connolly, Ph.D.**
Director of the Maryland Industrial Partnerships
University of Maryland
marthac@umd.edu

Maryland Technology Enterprise Institute (MTECH)

MTECH

At the Maryland Technology Enterprise Institute (Mtech),we focus on two things: possibilities and results. We offer programs, courses, workshops and competitions to help aspiring entrepreneurs learn how to bring their ideas and products to the world. We help faculty, student, and regional entrepreneurs create successful ventures. We help companies solve vital challenges and develop top-selling products that improve and save lives by connecting them with resources to succeed.

Our results: among our core programs, we have had a $25.7 billion impact on the Maryland economy since 1983. Top-selling products such as MedImmune's Synagis®, which protects infants from a deadly respiratory disease, and Hughes Communications' HughesNet®, which brings satellite-based, high-speed Internet access to the world, were developed through or enhanced by our programs. Billion dollar companies such as Martek Biosciences and Digene Corporation graduated from our incubator.

MTECH Entrepreneurship Education

At Mtech, we believe that a firm grasp of the entrepreneurial process and mind-set benefits every person engaged in developing technology. Our goal is to infuse technology-creating students, faculty members and professionals with that

knowledge and its accompanying skills. Armed with an entrepreneurial mind-set, technology creators drive economic growth by launching successful ventures and bringing life-changing products and services to market.

Hinman CEOs (www.hinmanceos.umd.edu)
Living-Learning Undergraduate Entrepreneurship Program

Featured on CNN and the recipient of numerous awards, Hinman CEOs is the nation's first living-learning entrepreneurship program, placing entrepreneurially minded students from all disciplines into a unique community in which students live together, learn about entrepreneurship through courses and an exclusive speaker series, and can launch new ventures. The program's on-site business coaching services, entrepreneurs-in-residence, $250,000 Impact Pre-Seed Fund and Hinman Alumni Fund provide a rich environment for launching new ventures. Incoming juniors are invited to apply for this competitive program. The mission of Hinman CEOs is to foster an entrepreneurial spirit, create a sense of community and cooperation, and develop ethical leaders. University alumnus and successful entrepreneur Brian Hinman provided $2.5 million to initiate and support the Program. More»

Hillman Entrepreneurs (www.hillman.umd.edu)
Four-Year Transfer Program to Create Entrepreneurial Leaders

The Hillman Entrepreneurs Program is an innovative educational initiative for transfer students who begin their study at the Prince George's Community College and complete their bachelor's degrees at the University of Maryland. This four-year scholarship program is targeted at students driven to be successful entrepreneurs and leaders in their communities. Hillman Entrepreneurs features a series of entrepreneurship and leadership courses, mentoring from full-time directors, networking opportunities and community-building activities. The program was established through a generous $1.7 million gift from the David H. and Suzanne D. Hillman Family Foundation. More»

Entrepreneurship and Innovation Program (www.mtech.umd.edu/educate/eip.html)
Living-Learning Entrepreneurship Program for Academically Talented Freshman and Sophomore Students

The Entrepreneurship and Innovation Program provides freshmen and sophomores from all majors the opportunity to learn and live entrepreneurship and innovation. Students develop the entrepreneurial mindsets, skill sets, and relationships to launch successful concepts with startup

companies and corporate ventures. This new Honors College program will launch fall 2010. Through experiential learning, dynamic courses, seminars, workshops, competitions, and volunteerism, students receive a world-class education in entrepreneurship and innovation. In collaboration with faculty and mentors who have successfully launched new ventures, all student teams develop an innovative idea and write a product plan. More»

Young Scholars Discovery (oes.umd.edu/index.php?slab=entrepreneurship)
Summer Course for Current Seventh or Eighth Grade Students Interested Entrepreneurship

Young Scholars Discovery welcomes rising eighth and ninth grade middle school students to an exceptional learning opportunity at the University of Maryland. For two challenging weeks, Discovery nurtures academically talented students who share similar interests, abilities, and goals. Discovery scholars explore new ideas, acquire skills and knowledge, and learn about career opportunities. Innovative faculty provide dynamic instruction and encourage interactive problem solving. This summer, discover, explore, grow, and learn about university life at Maryland with Young Scholars Discovery! Mtech's Young Scholars Discovery course is EXST 011, Designing Your Own Business, which teaches students the basic business, strategy, and leadership skills needed to launch new ventures. More»

Young Scholars Program (www.mtech.umd.edu/educate/ysp/)
Summer Courses for High School Students Interested in Entrepreneurship, High-Tech Marketing and Biopharmaceutical Production

The Young Scholars Program invites high school students from throughout the U.S. and the world to an amazing pre-college experience at the University of Maryland. Rising high school sophomores, juniors, and seniors with exceptional ability and promise pursue academic interests, discover career opportunities, and earn three university credits. This summer, be part of an international, multicultural community and experience university life at Maryland. Mtech's summer 2011 Young Scholars courses include: ENES 140, Discovering New Ventures - Foundations in Entrepreneurship; ENES 141, Introduction to High-Tech Product Development and Marketing; and BIOE 160, Biopharmaceutical Production. More»

Entrepreneurship Courses (www.mtech.umd.edu/educate/courses/index.html)

Whether you're in middle school, high school, an undergraduate, a graduate student, or a corporate executive, Mtech offers a broad array of entrepreneurship and innovation courses tailored for you.

Mtech is hosting free office hours to help aspiring and current entrepreneurs with tech-based startups or ideas get advice on how to:

- build and finance a startup company
- develop and protect intellectual property
- navigate the technology transfer process
- refine your business strategy for rapid growth
- tap into other entrepreneurial resources

Representatives from the following organizations and groups are typically on hand to speak with you one-on-one regarding any questions you might have about starting a company:

- Mtech VentureAccelerator Program
- Mtech Technology Advancement Program
- Office of Technology Commercialization
- Dingman Center for Entrepreneurship
- Maryland Intellectual Property Legal Resource Center
- Maryland Biotechnology Center
- Experienced Entrepreneurs
- Representatives from the following investment and grant organizations are also often on campus to participate in Entrepreneur Office Hours or other Mtech events for new ventures: CNF Investment, New Markets Growth Fund, Amplifier Venture Partners, LP, Novak Biddle Venture Partners, HIG Ventures, Grotech, Maryland Venture Fund, and TEDCO.

Mtech hosts Entrepreneur Office Hours on the second Tuesday of every month, from 10:00 a.m. to noon, in room 1103 of the Technology Advancement Program building.

Entrepreneur Office Hours was started in 2005 by The Office of Technology Commercialization in the College of Chemical and Life Sciences (CLS). In 2007, Mtech partnered with OTC to expand Entrepreneur Office Hours to all colleges within the university as well as entrepreneurs from the DC/Baltimore region.

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December 6, 2011

The White House
Office of Science and Technology Policy
Executive Office of the President
725 17th Street, N.W., Room 5228
Washington, D.C. 20502
BIOECONOMY@OSTP.GOV

Re: Request for Information: Building A 21st Century Bioeconomy

Dear Sir or Madam:

We submit these comments on behalf of Cook Group Inc. (Cook). Cook is a holding company of international corporations engaged in the manufacture of diagnostic and interventional products for radiology, cardiology, urology, gynecology, gastroenterology, wound care, emergency medicine, and surgery. Cook pioneered the development of products used in the Seldinger technique for angiography, and in techniques for interventional radiology and cardiology. Our products benefit patients by providing doctors with a means of diagnosis and intervention using minimally invasive techniques, as well as by providing innovative products for surgical applications. Cook sells more than 15,000 different products, which can be purchased in more than 60,000 combinations.

Our company employs about 10,000 people around the world. Eight thousand of those are based in the United States. While 50 percent of our products are sold outside the United States, 85 percent are manufactured in this country.

We commend the President and the Administration for recognizing the importance of the Bioeconomy. The U.S. is the world leader in biotechnology, and we believe it is critical that the nation do everything possible to promote and expand the biotech industry if our nation is to compete economically during the rest of this century and to ensure our citizens have the best available health care.

The medical device industry is an important segment of the bioeconomy. It employs nearly 500,000 people manufacturing products that save or improve the lives of millions of Americans and generates a trade surplus in excess of $5 billion. Salaries in the device industry average $58,000, according to the Department of Commerce. Further, it is an environmentally clean industry. Developing public policies that promote growth in this industry is exactly what our government should be doing as we struggle to emerge from a deep recession.

We welcome the opportunity to provide information addressing specific issues raised in the Request for Information. Before doing so, however, we would like to provide general background information, which we think is urgently important.

While the medical technology industry has been one of the jewels in the American economy, its position as a global leader is eroding. This will undoubtedly affect the ability of Americans to access future break-through medical advancements and the growth of U.S. jobs. A recent study found that in the future, China, India and Brazil will experience the strongest gains in developing next generation lifesaving products. Without changes to U.S. policies, these gains will move capital, jobs, and research away from the U.S. and toward these growing markets. (Source: "Medical Technology Innovation Scorecard: The Race for Global Leadership," PwC, January 2011).

There are several policies that are driving American medical device companies to seek clinical data and manufacture and launch new products outside of the United States.

1) Imposition of a new, 2.3% excise tax on the sale of medical devices. This tax is levied on domestic sales, not profits. For a typical, larger medical device manufacturer, the tax will be a burden of 15-20% on earnings (in addition to federal and state corporate taxes). To smaller start-up companies not yet making a profit, it will be an additional cost that must be financed. While the tax will also be assessed on imported products, profits from those products will be subject to a much lower corporate rate in foreign countries. This increases pressures to move production abroad.

2) An FDA regulatory environment that is painfully slow and risk averse despite strong safety records. In stark contrast, the European system is more transparent, timely and predictable.

3) A U.S. corporate tax structure that is one of the highest in the world, second only to Japan.

4) Cynicism regarding the proper roles of health professionals, academia, government and industry and the relationships among these important stakeholders.

All of these policies must be addressed to reverse the trends faced in developing new medical technology. We recognize that the central focus of the Request for Information is narrower, but we hope that the Office will include all important policies in its "Bioeconomy Blueprint."

In response to question 15 of the Request for Information regarding improvements in the regulatory processes for medical devices, we are attaching a list of specific suggestions for changes that FDA could make to improve its performance. Although the list is lengthy, we

believe that all of the recommendations are important, not only to the Bioeconomy, but to patient health care as well. We have been communicating with FDA on a regular basis concerning these suggestions and believe the Office of Science and Technology Policy should also be aware of them.

In reviewing this list, it is important to keep in mind the unique nature of the process in which medical devices are developed, which is quite different from that of pharmaceuticals. The device development process is for the most part evolutionary, with incremental changes, rather than revolutionary. When a device is introduced doctors use it. Some will come up with ideas to modify the device in minor ways to improve its performance or to allow them to use it for slightly different anatomy or indications. These changes are made and this in turn leads to more ideas from physicians that lead to more changes and so on. This incremental and collaborative process has led to steady improvements in technology, which over an amazingly short period of time, have led to a revolution in the practice of medicine. The keys to this evolutionary approach have been close collaboration between medical device users (physicians) and medical device developers (industry) and a medical device regulatory structure that recognizes the value of building new medical devices upon the foundation of those that are on the market and have a solid history of safe and effective use.

Further, it is important to recognize that levels of regulation should reflect risk associated with a specific device and that the system must be flexible to changes in risk that occur as we gain experience with a technology. There are many questions that need to be answered with a new medical treatment using novel technology, but as it is used by thousands of physicians to help their patients, there are fewer and fewer questions that arise. It is wasteful to require industry scientists to reprove the answers to questions that are already known, and it is wasteful to require FDA scientists to review the same evidence over and over again.

It is also critical for regulatory policy to accommodate the realities of the marketplace for medical devices. It is relatively small compared to drugs as devices are generally used to treat acute problems in hospital settings rather than to treat millions of patients over periods of years and decades. The markets for most devices used in new treatments simply will not economically support overly large clinical studies, which are limited in value anyway because the success or failure of devices is largely dependent on the ability of thousands of physicians to use approved devices in their every day practice. Experience in using devices over time provides the most reliable clinical data. Finally, while relatively small, the marketplace is global and regulatory policy must permit American manufacturers to be nimble and react to developments occurring around the world.

We hope our suggestions are helpful, but we must note that improving the regulations will not solve the most pressing problems. FDA must properly manage its operations and ensure that the

regulations are used properly. In recent years, there has been inconsistency in the review process at all levels and an alarming lack of understanding of regulatory requirements within the agency. Further, we have encountered major changes in previously agreed to requirements for our studies made by FDA with no scientific justification, and these have significantly delayed approval for several important products. Indeed, the uncertainties and delays at FDA have left our company no choice but to introduce most all of our new products outside the United States long before American patients can have access to them. To reverse this trend, leadership at FDA is critical. Staff needs to be properly trained and supervised, and the culture needs to change to recognize the importance of bringing new medical treatments to patients. With the firm commitment of leadership, there is no reason why FDA cannot approve or clear most products as quickly as any nation in the world.

Finally, we would like to comment on the importance of public and private collaboration, which is raised in the Request for Information. Innovation can start with breakthroughs in basic or applied science in government laboratories, in research programs in academic settings, and in private industry. Then it proceeds to the development of a concept for a product, design, prototyping, testing, then finally approval to market, manufacturing, training providers, and widespread use. These stages involve physicians, hospitals, academic institutions, government and, very importantly, industry. Then once a product reaches the market, it generates new ideas, most often among physicians, which lead back to industry and back into product development, testing, clinical trials, approvals, etc. It is critical that as we go forward all of the necessary stakeholders be enabled to make their contributions to this time-tested process.

Sadly, in the last several years, we have seen a growing cynicism regarding the role of industry in the development of medical technology. This is undermining our country's ability to achieve the potential benefits of the medical revolution we are experiencing. Specialty societies are distancing themselves from the very manufacturers that have provided their members with the cutting edge tools to help patients and teach them how to effectively use those tools. Regardless of structure, industry sponsored research (which comprises the majority of medical research) is denigrated. Inventors of breakthrough technologies are ostracized for receiving royalties on their inventions. Academic institutions are threatening to turn away industry-sponsored research which is absolutely essential (and often required) to develop and approve products. In our view, all of this could lead to incalculable harm to patients as new technologies are delayed, never reach the drawing board, or perhaps developed but never implemented in clinical practice. This development is not serving patients' needs.

Surely we can find a way to develop common sense rules and use transparency so that as a nation we can fully utilize all the resources available (health care providers, academia and industry) to bring new technologies to patients. We believe that government is the appropriate party to bring

all stakeholders together and to help develop consensus in this area. It would be tragic if we squander the wonderful opportunity before us.

With this said and the importance of collaboration noted, we believe it is important that FDA recognize the areas where it can be helpful and where it is likely that its contribution will be marginal. For example, the agency has recently proposed to construct a core curriculum for medical device development as part of the effort to promote innovation. As mentioned above, the American medical technology industry is the most innovative and creative in the world. Its members know how to develop new medical devices. At a time when resources are scarce, we think it would be wise for the agency to focus on areas where it has significant expertise.

Thank you very much for considering our thoughts. We wish you the very best in developing the Blueprint. This is a very important endeavor and do not hesitate to call upon us if we can be helpful in any way.

Respectfully,

Stephen L. Ferguson
Chairman of the Board

Attachment: Suggestions for Improving Performance at FDA

SUGGESTIONS FOR IMPROVING PERFORMANCE AT FDA

1. **Focusing on the mission.** The mission of the FDA is to protect and promote the public health. FDA processes and activities that do not further this mission and do not help patients should be modified or eliminated. In the course of these recommendations, we point out several areas where the processes or actions of the agency are not productive. We believe such processes and activities should be reformed or eliminated administratively or legislatively if necessary. Achieving such changes should be FDA's top priority.

2. **Recruiting and training staff.** The agency has experienced significant staff turnover in recent years, as have many private and public organizations. Like all organizations, it must develop **systems** that address recruitment and training if it is to effectively carry out its mission despite such problems. We are pleased that FDA's Center for Devices and Radiological Health (CDRH) is developing a certification program for reviewers, among other things. Training is essential if we are to minimize the inconsistencies that are bogging down agency reviews and to improve the quality of reviews. In the past, Cook has invited CDRH device reviewers to visit our facilities independent from any pending product reviews so that they can gain a better perspective on how medical device companies develop and manufacture products. Feedback from both reviewers and management was very positive, with participating reviewers gaining valuable insights into the development process. We recommend that FDA implement a formal program that assures one third of reviewers each year visit a company that makes products in the reviewers' areas.

3. **Improving the process of investigational device exemptions (IDEs).**
   - **Approval requirements.** The investigational device exemption was intended to allow distribution of a device so its safety and effectiveness could be studied. An approval of an IDE is not an approval of a product or a commitment that the approved study will result in an approval or clearance for commercial marketing by FDA.
     - It has become common for FDA to treat an application for an IDE as if it were the application for Premarket Approval (PMA) that may eventually arise from the proposed clinical study.
     - It is important that reviewers recognize the difference between the two applications. The IDE is simply a study to learn about the device. It is impossible to know the answers to all of the questions that are critical to the PMA until the study is done. Indeed, in many instances, the study will not result in a PMA. Focusing on issues related to a possible subsequent PMA causes lengthy delays in starting studies for which all relevant safety questions have been answered. Training review staff in these distinctions should be a priority.
     - While it is helpful to receive advice on items that may be of importance to FDA in a subsequent marketing application, including this advice within the formal FDA response to the IDE application frequently causes needless delays in Institutional Review Board (IRB) approval of the investigation. We recommend that FDA use a separate mechanism (e.g., a separate letter) to communicate this advice to sponsors so that clinical studies may commence upon receipt of the notification.
   - **Conditional approvals.** The practice of conditional approvals of IDE applications, although well intended, has led to confusion and delays.

- IRBs are extremely sensitive to regulatory compliance issues, and not infrequently they refuse to allow their institutions to participate in studies that have been "conditionally" approved, even though the conditions are by definition unrelated to the assurance of safety necessary to initiate the study.
- We recommend that separate letters be written, one approving the commencement of the IDE clinical study, the second addressing any ongoing deficiency questions.

- **National IRBs.** We recommend that the agency require all institutions to accept an approval by a national IRB in cases where a device sponsor has chosen to use this approach. We would also encourage the FDA and HHS to review the regulations governing the IRBs to ensure that institutions are able to accept the national IRB determinations.

4. **Stabilizing the moving goal posts.** A major problem faced by manufacturers in the premarket review process arises when changes are required by FDA in a clinical study despite previous agreement on the study protocol. It has been our experience that in many cases such changes are not based on strong scientific or public health grounds. We recommend that FDA not permit changes unless specific, scientific evidence demonstrates the clear necessity of the change to protect the public health.

5. **Utilizing international standards.** Standards are invaluable in expediting the approval and clearance processes and represent the consensus of world-wide experts. They significantly reduce or eliminate the need to repeatedly prove basic principles. While the FDA has often been involved in the development and writing of international standards, it has been slow to adopt them. In many cases, FDA issues its own guidance rather than recognizing an established international standard. International standards may also avoid the use of FDA resources in developing guidance documents. We recommend legislation that would permit anyone to petition for the recognition of one or more standards and require the FDA to recognize such standards within 180 days or state its reason(s) for not doing so.

6. **Utilizing information from premarket applications.** Until 1990, the Food, Drug, and Cosmetic Act (FDCA) did not permit the Secretary to utilize in any way information learned from premarket applications in approving other applications. In 1990, Congress amended the Act by passing Section 520(h)(4) to allow the use (but not disclosure) of such information in approving an application for another device after the publication in the Federal Register of an approval of an application for the fourth device "of a kind." The purpose of this provision was to reduce the waste of agency and industry time and resources, reduce the unnecessary sacrifice of animals, and reduce the number of human patients subjected to clinical trials as manufacturers are required to prove principles over and over again that had already been proven. Unfortunately, this provision proved too cumbersome and was never used. In 1997, Congress amended the Section to permit information from a PMA to be used six years after the approval of the particular application for several purposes, including the approval of another application. Again, the provision has proved too difficult to use.
    - It is most unfortunate that our laws have prohibited FDA from using what it has learned so that it can focus on important unanswered questions presented by a new technology. Instead, the current system requires highly skilled scientists both at FDA and in industry to expend resources dealing repeatedly with the same questions, which are really no longer meaningful questions. Further, this prohibition of using information inhibits the ability to

employ modern techniques of statistical analysis. The net result of all of this is major delay in the approval process to the detriment of patients badly in need of new therapies.

- We recommend legislation to eliminate these restrictions, which are simply barriers to entry. While trade secrets and legitimate proprietary information should be protected from disclosure and patents enforced, the FDA should be permitted to apply what it knows and expedite the process of innovation.

7. **Utilizing foreign data.** A tendency has developed within FDA to reject information developed in studies outside the U.S. that were not approved by the FDA prior to their execution. It should be made clear that valid scientific evidence is valid scientific evidence regardless of where it was originated or whether the studies were pre-approved by the agency. In regard to foreign data, it is particularly important for FDA to recognize that study protocol requirements may differ from nation to nation because of cultural or other differences. Data should not be rejected simply because the design of a protocol is different from what FDA would prefer, as long as critical patient protections are included and data gathered from the study provide robust scientific evidence for determining the safety and effectiveness of the device in question. It is clear that the international medical community recognizes published literature from around the world to assess appropriate medical care for patients. FDA should do likewise for foreign clinical studies submitted by sponsors.

8. **Taking the lead in international harmonization.** Medical devices markets are global markets, and there is a tremendous waste of resources in bringing products to market when countries have significantly different approval/clearance processes. The leadership of the U.S. is critical to developing a more harmonized global system. Specifically FDA should work to--
    - Strengthen the Global Harmonization Task Force (GHTF) and its successor organization the International Medical Device Regulators IMDRF), recognizing that industry participation is critical to success, because it is industry which bears the economic burden of complying with multiple regulatory systems as it brings new products to patients.
    - Develop a system that provides for a single approval or clearance for moderate risk (Class I and II) devices around the world.
    - Develop common standards for clinical trials that are universally accepted for approval purposes.
    - Develop an inspection process that is accepted by all regulatory authorities.
    - Develop a system that promotes adherence to international standards.

9. **Using alternatives to clinical trials.** Clinical trials should be avoided wherever there are alternative ways of providing information necessary to demonstrate a reasonable assurance of safety and effectiveness. This can be accomplished by using historical data, confirmatory studies, registries, animal studies, databases and the latest technologies in testing and computer modeling. The revolution in information technology provides us with the tools to appropriately aggregate and analyze the goldmine of data that government agencies (such as FDA, CMS, NIH, and DOD), health plans, health care providers and private industry already have available. In years to come, that data will be enriched many times over as electronic medical records become universal. This information can be used to minimize the need for clinical trials and in many instances the sacrifice of animals. It can answer many postmarket questions as well. FDA has recognized the importance of developing alternatives to clinical trials, yet on August 15, 2011, it published a draft guidance

calling for the increased use of randomized, blinded trials. The FDA needs to clarify its position and move to solutions not involving clinical trials wherever possible.

10. **Improving the humanitarian device exemption (HDE).** The HDE provides a mechanism to bring novel products for small patient populations to the marketplace. While patients have been provided access to many important products since the provision was enacted in 1990, the process has been limited by two restrictions: the profit prohibition and the 4,000 patient ceiling. In 2007, Congress removed the profit prohibition on HDEs for pediatric products and this change has led to a significant increase in applications for such exemptions, but problems remain. For instance, although pediatric devices can be sold at a profit, the sales are limited to an "Annual Distribution Number" that does not allow for patients who may need more than one device (i.e., a course of treatment) in order to be treated for their condition. We recommend the profit prohibition be eliminated for all HDEs by Congress and the concept of the "Annual Distribution Number" be eliminated. We also believe the patient ceiling should be raised to a number that represents a patient population large enough, as a practical matter, to populate a meaningful clinical trial. The current ceiling was established arbitrarily, and making this change would give it a rational basis and carry out Congressional intent to utilize the HDE where alternative approval mechanisms are impractical. Note: H.R. 3211, introduced by Rep. Bass, addresses the profit prohibition.

11. **Improving de novo classification.** De novo classification was added to the law in 1997, to fill in a gap in the approval/clearance process. There are a number of novel products that are moderate risk for which the premarket approval process is not warranted. Unfortunately, a relatively small number of products has been classified by the de novo mechanism. We recommend that the process be streamlined by eliminating the need for a formal finding of "not substantially equivalent." We also recommend that the elements that should normally be considered in the de novo process are: (a) an assessment of clinical evidence that is available and pertinent to the new device, (b) a discussion of how the risks are to be minimized, (c) a discussion of what additional clinical data, if any, must be collected to properly assess the risks, and (d) an analysis of the benefit to risk ratio of the device. Note: H.R. 3203, introduced by Rep. Bilbray, addresses the issue of requiring a formal, not substantially equivalent decision.

12. **Effective use of postmarket surveillance and studies.** Postmarket surveillance is another important aspect of the regulatory scheme for medical devices. No matter how thorough, the approval process is limited and will not detect every possible outcome from the use of a device. It is not until products are used by hundreds or thousands of physicians over a period of time for the treatment of patients with a variety of co-morbidities that we gain a broader knowledge of devices. For this reason, it is important to follow devices closely over the first few years after they are launched. For most products, which are evolutionary in nature, this is not difficult. Surveillance amounts to diligent monitoring that is best aided by a robust system of adverse event reporting. For the rare devices that are revolutionary, a more active program may be appropriate.
    - In recent years, FDA has treated most Class III products as revolutionary rather than evolutionary, when in fact most are very similar to products already on the market. These products should be well suited to simple surveillance. Requirements for unnecessary clinical studies consume immense resources from FDA, industry, and health care providers that should be used for other purposes.

- Postmarket clinical studies present a number of problems and should be required sparingly:
    - If there are several similar devices on the market with the same indications, in many instances there will not be enough available patients to populate the studies. The markets for devices are not like those for drugs in size. When several companies are seeking patients for postmarket studies, they will have great problems in finding patients and be unable to fulfill the obligations FDA has imposed.
    - Doctors are generally not interested in participating in studies regarding devices that have already been proven to be safe and effective and approved for commercial distribution. They prefer to study new, cutting edge products, where it is more likely that the study will provide new knowledge. This adds to the challenges facing the manufacturer trying to conduct postmarket studies.
    - Prolonged studies can subject patients to added interventions and risks (e.g., imaging contrast and exposure to radiation) that would not be consistent with the routine standard of care.
    - Because of the rapid development of technologies, new, improved, next generation devices often become available during the term of postmarket studies. Using an older device when better products are available or when the stipulations of the postmarket studies are not consistent with the standard of care, presents further ethical difficulties for physicians. In addition, when the longer term data are complete, they often represent the performance of a device that is no longer marketed.
- FDA should issue clear guidance that postmarket studies are appropriate only for a limited number of devices, such as new, revolutionary devices that are implants or used in new medical treatments, rather than those follow-on devices where knowledge has accumulated. Further, FDA should utilize analyses of databases, extended patient follow up, or registries whenever possible.

13. **Efficient reporting on postmarket studies.** Manufacturers of products that have been approved through the PMA process face several reporting requirements that are often redundant. If the studies conducted under the IDE are continuing, and they often are, periodic progress reports are required. If an additional study was required as a condition of approval, progress reports on that study must also be made. And, in all instances, an annual report must be filed on the device. There is significant overlap in the information contained in all of these reports, and preparing and reviewing repetitive reports is tedious and resource intensive. To reduce this redundancy and to conserve industry and agency resources and time, we believe FDA should review the information that must be reported, eliminate requirements to report information that has questionable value, and design a consolidated report that could be filed on an annual basis.

14. **Efficient regulation of modifications to medical devices.** Medical devices are constantly modified and most modifications are very minor. Such changes are tested, documented and approved internally by manufacturers under the quality system regulation. This works well. Unfortunately, FDA has issued a new guidance that we believe will dramatically increase the number of 510(k)s filed. We recommend that guidance be withdrawn. Unless there is a significant chance that a particular change will impact safety or effectiveness, the processing of such changes

is best left to the quality system. If FDA insists on taking an expansive view of the types of changes that generate the need to file a 510(k), it will waste precious resources that are best directed to much more important issues. Indeed, it would not be unusual for a company with a broad range of products to have more than 1,000 modifications in a year. Expanding its review of such changes could overwhelm CDRH and shut the system down. If the current guidance needs to be updated, we recommend the stakeholders be brought together to develop a more practical approach.

15. **Utilizing authority to down classify well known medical devices.** As experience is gained with a medical device, the questions that were legitimately asked during the approval process become fully answered. When this occurs, the agency should down classify the product to save resources to focus on the next generation of new, cutting edge technologies. Such down classification rarely happens, however. The agency does not give such action a high priority, and it is a cumbersome process which can take five to ten years. For example, a down classification petition was submitted to the Agency on August 28, 2000 and filed by FDA on September 21, 2000, the Circulatory System Devices Panel recommended on December 4, 2000 that certain PTCA catheters be reclassified from class III to class II with special controls, and it was not until a decade later that FDA issued the Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters Document on September 8, 2010 (75 FR 54496, Sept. 8, 2010). To emphasize the importance of reclassification to the efficiency of the agency, we recommend legislation to authorize the agency to publish a list of products to be down classified, receive and review comments for 90 days, and then issue a rule classifying the products appropriately.

16. **Exempting products from the requirements of the 510(k) clearance process.** Experience in using a device also provides knowledge about moderate risk products that obviates the need for the filing of 510(k)s. Clear authority should be given the agency to periodically list such products, receive comments for 60 days and then issue a rule exempting them from the requirements.

17. **Inspecting efficiently.** We believe that inspections are extremely important. They make certain that manufacturers are adhering to their quality systems. Congress expected FDA to routinely inspect each manufacturer every two years. This has not happened. Fortunately, countries in Europe and elsewhere require inspections every year and this has helped to fill any void left by FDA. These inspections are usually conducted by third parties known as notified bodies. It is important to recognize current practices and take advantage of them. Congress should instruct FDA to make it a top priority to work with other nations to develop a common protocol for inspections accepted by all nations, and it should accept inspections by third parties. The requirements for inspecting every 2 years should be lengthened to every 4 years. Further, premarket inspections should not be required for companies that have been favorably inspected within one year.

18. **Utilizing third party review.** Congress authorized the agency to establish and use a third party review system for certain low-risk products. Unfortunately, third party review has not flourished. A major reason for this is that third parties are not given adequate access to information regarding predicate devices. We recommend legislation to grant such access. Further, we believe Congress should instruct the agency to give high priority to working with other nations to develop a system that provides for a single approval or clearance for moderate-risk devices (Class I and II) around

the world. Note: H.R. 3205, introduced by Rep. Paulsen, addresses in part the issue of access to information.

19. **Utilizing quarterly malfunction reporting.** Section 519(a)(1)(B) of the FDCA) requires promulgation of a regulation to provide criteria for quarterly reporting of malfunctions of moderate-risk devices in a summary format. Though this requirement was enacted by Congress in 2007, FDA has not implemented it. FDA receives thousands of malfunction reports, which overwhelm the device reporting system. Filing those reports consumes significant resources of manufacturers and attempting to review them consumes significant resources of the agency. We recommend that FDA should immediately issue regulations to implement Section 519(a) to dramatically reduce the number of individual reports submitted to the agency while maintaining full accountability from manufacturers to report every malfunction reported currently, but on a quarterly basis and in summary format that will provide FDA useful and manageable information from malfunction reporting.

20. **Revamping user reporting.** Section 519(b)(5) of the FDCA requires the Secretary to designate sentinel device user facilities to assume the responsibility for user reporting of adverse events with devices. While the agency has developed a program for user facilities known as MedSun, it has not fully implemented the program so that additional user reporting can be dispensed with. It is common knowledge that the current user reporting system is not working. At best, the agency receives a small portion of the reports that the statute requires, and then those received are not satisfactorily analyzed. Programs that do not provide value should be eliminated or replaced. This can be done by following the current statutory requirements. FDA should propose a regulation to implement the sentinel reporting system envisioned by Congress. Sentinel reporting would be based on strategically selected healthcare centers that would provide a representative profile of user reports for device deaths and serious illnesses or serious injuries. Members of MedSun would be excellent candidates for this program. Sentinel facilities would have the expertise to provide meaningful reports with useful analyses and add value to the system. They could also be given special recognition for their contribution to patient safety. Once the system is in place, the sentinel reporting could replace the general requirements for user reporting, as Congress directed, with a more robust system in which obligations are well understood and enforceable.

21. **Inspecting contract manufacturers of drugs and biologics.** Currently FDA inspects contract manufacturing organizations (CMOs) only when they have contracts to manufacture specific products. This can significantly delay the utilization of new contract facilities, as proprietary companies are reluctant to enter a contract with a CMO that has never been inspected. In view of the current drug shortages, it is essential that all manufacturing capabilities be made available as soon as possible. Since a major portion of the inspection is general in nature and does not relate to a specific product, FDA should conduct a general inspection of CMOs requesting such inspection as soon as possible, to make it clear that new, high-quality manufacturing capacity is available. This will speed the process of bringing that capacity into operation and assist the country in supplying badly needed pharmaceuticals to patients.

22. **Obtaining advice from outside.** Just as medical device manufacturers benefit from inspections and audits, so, too, could FDA. We recommend that FDA promptly retain an outside consulting firm to audit its operations and to make recommendations aimed at improving the agency's

performance and efficiency. Note: S. 1700, introduced by Sen. Klobuchar, would require a similar audit.

AMERICAN SOCIETY FOR MICROBIOLOGY

Response to Bioeconomy Blueprint RFI
American Society for Microbiology
December 6, 2011

The American Society for Microbiology (ASM) welcomes the opportunity to respond to the OSTP's request for comment on the development of the National Bioeconomy Blueprint. ASM represents nearly 40,000 microbiologists with a remarkably broad range of expertise, as befits a group studying Earth's most diverse and prolific life forms.

Microbes are essential to the emerging bioeconomy. Why? Because they are:

- A virtually inexhaustible source of biodiversity, metabolic ingenuity, and natural products;
- Workhorses for the production of industrial catalysts and pharmaceuticals from insulin to antibiotics to vaccines to probiotics;
- A promising source of the next generation of environmentally and politically neutral fuels;
- Required partners for all plant growth, making microbes an untapped resource for adapting crops to grow in more places with fewer inputs;
- Critical drivers of the Earth's biogeochemical cycles and therefore important players in the climate change realm, both as sentinels and, potentially, as mitigators;
- Providers of the chassis and parts sets for synthetic biology;
- The ultimate model organisms for molecular and cellular biology, making possible the spectacular advances in health and biotechnology born out of those disciplines.

Microbes are even more significant when we consider the economically and socially critical health care sector. Interactions between humans and microbes are essential to our well-being, most notably in areas that do not involve the role of microbes in infectious diseases. The vast and beneficial microbial communities that live in our guts and on our skin have profound effects on metabolism, immunity, and behavior. Understanding the role of our microbial partners is crucial to treatment of allergies, asthma, obesity, and auto-immune disorders. Thus, in-depth investigation of the central role microbes play in these and other conditions is vital to the development of novel therapeutics.

In short, if America is going to build a thriving bioeconomy, its success will hinge on understanding and development of the capabilities of the microbial world.

In recent years, numerous groups that span diverse scientific disciplines have proposed sets of "Grand Challenges" that humanity faces. What is particularly striking is the clear consensus that microbial sciences are crucial to meeting the majority of these challenges irrespective of the scientific group putting forward the challenge. We refer the reader to the box outlining a small sample of challenges from the Gates Foundation and other organizations and fields. We note that many other grand challenges from these and other organizations rely on microbial sciences. Indeed, in the recent National Academies report, "A New Biology for the 21st Century" all four of the suggested grand challenges have significant microbiological components. The imperative for microbiologists today is not to articulate microbiology's grand challenges, but rather to ensure that microbes' contributions to the nation's bioeconomy blueprint are fully realized.

Samples of Grand Challenges that rely on microbial science:

The Gates Foundation *Grand Challenges in Global Health*:

- Create effective single dose vaccines that can be used soon after birth
- Devise reliable tests in model systems to evaluate live attenuated vaccines
- Learn which immunological responses provide protective immunity
- Develop a biological strategy to incapacitate a disease-transmitting insect population
- Create a full range of optimal, bioavailable nutrients in a single staple plant species
- Discover drugs and delivery systems that minimize the likelihood of resistant microorganisms
- Create therapies that can cure latent infection
- Create immunological methods that can cure chronic infections
- Develop technologies that permit quantitative assessment of population health status
- Develop technologies to allow assessment of many conditions and pathogens at point-of-care

Grand Challenges for Engineering (National Academy of Engineering)

- Make solar energy economical
- Develop carbon sequestration methods
- Manage the nitrogen cycle
- Provide access to clean water
- Engineer better medicines

A New Biology for the 21st Century (NRC, 2009)

- Food: Generate food plants to adapt and grow sustainably in changing environments
- Health: Understand individual health
- Energy: Expand sustainable alternatives to fossil fuels
- Environment: Understand and sustain ecosystem function and biodiversity in the face of rapid change

New Horizons in Plant Biology (NRC 2008)

- A scalable view of global regulatory networks arrived at by collection of system-wide data sets from naturally variable genotypes assessed across growth and stress conditions, and in association with other organisms
- Families of models incorporating these datasets that both describe system behavior and predict outcomes of subsequent system perturbations
- Validate computational representations of individual plant cells, tissues, and, eventually, whole plants interacting within their multiorganismal communities

From Molecules to Minds: challenges for the 21st century (IOM 2008)

- How does the interplay of biology and experience shape our brains and make us who we are today?

Grand Challenges in Environmental Science (NRC 2001)

- Understand how the Earth's biogeochemical cycles are being perturbed by human activities
- Understand the regulation and functional consequences of biological diversity, and to develop approaches for sustaining this diversity and the ecosystem functioning that depends on it
- Increase our ability to predict climate variability to understand how this variability may change
- Predict changes in freshwater resources and the environment caused by floods, droughts, sedimentation, and contamination in a context of growing demand on water resources
- Understand the ecological and evolutionary aspects of infectious diseases
- Develop a systematic understanding of changes in land uses and land covers that are critical to biogeochemical cycling, ecosystem functioning and services, and human welfare
- Develop a quantitative understanding of the global budgets and cycles of key materials used by humanity and of how the life cycles of these materials may be modified

The microbial sciences are highly interdisciplinary, incorporating, for example, molecular biology, cellular biology, physics, geology, chemistry, materials sciences, and engineering. This rich history is emblematic of a profound and general change in science and technology over the past 20 years. The interdependence of scientific and engineering disciplines and the potential advantages of interdisciplinary collaboration have never been greater. Yet, the traditional organizational structures of academia and government continue to make collaboration difficult. Building a sustainable bioeconomy will require integrating expertise across disciplines and reducing the existing barriers that discourage academia, industry, and government from working together to achieve common goals. The OSTP's RFI asks for input on such questions as what grand challenges the bioeconomy could tackle, what federal funding priorities will be needed to achieve the bioeconomy, what technical challenges must be solved, how the private, public and academic sectors can best work together, and how graduate training should evolve to meet the needs of the future. Without mechanisms to convene all of the different stakeholders who can contribute to meeting a grand challenge, advancing an industry, or developing a new technology the blueprint will fail. As a Society, we stand ready to help, by identifying microbial scientists to contribute to any such community consensus-building mechanisms, by helping to improve communication across microbial programs housed in different agencies, and by mobilizing our members to embrace and contribute to the development of a lasting bioeconomy.

Three areas seem particularly crucial to success. First, the efficiency resulting from coordination and communication across the federal government has the potential to multiply the value of all research funded by different agencies. Discoveries made by microbiologists working on optimizing biofuel production could propel the research of microbiologists studying human health, and the fundamental research on microbial physiology and ecology supported by the NSF could be translated into revolutions in applied research in multiple areas. However, it is difficult at present for these communities to benefit from each other's advances, form productive collaborations, or identify common infrastructural needs and transformative technologies. As a result, the US is not reaping the full value of federal investment in research. This problem is not unique to microbiology, but because of the inherent interdisciplinary nature of microbiology and its impact on all realms of the emerging bioeconomy, microbiology could serve as an excellent prototype for the development of cross-agency communication and coordination endeavors. Again, the ASM would be eager to identify appropriate individuals from across the field of microbiology to contribute to such an effort.

Building bridges for communication across microbiological communities would begin to address a second, fundamental need: identifying and developing infrastructural resources that would benefit most if not all scientists. Again, we offer microbiology as a model for all disciplines. From highly transparent, searchable and manipulable databanks, to new imaging and high-throughput spectroscopy technologies, to long-term environmental data collection efforts, many investments exceed the scope and resources of any one federal agency, but collectively funding them would improve the productivity of all scientists and leverage the value of their combined research. Identifying and jointly investing in such infrastructural projects would speed the emergence of a bioeconomy.

Third, the Society agrees that focused grand challenges are essential as they can have a transformative effect, often well beyond their stated goals. The Human Genome Project provides a perfect example: the technological advances spurred by that project revolutionized microbiology, revealing a treasure trove of microbes that were invisible before inexpensive, high-throughput sequencing made it possible to detect the microbes that live everywhere on Earth, but do not grow easily in laboratories. In turn, this newly discovered microbial diversity has contributed to advances in bioremediation, natural product discovery, biofuel production and many other applications. Microbiology is poised to make huge contributions to such challenges as increasing crop productivity with fewer inputs and sustainable production of liquid fuels. Irrespective of the grand challenges that are selected as the pillars of the bioeconomy blueprint, the ASM is certain that

microbiology will be central to its success, and we look forward to contributing our effort and talent to making the blueprint a reality.

Finally, through its colloquium program, the American Academy of Microbiology has explored the role of microbiology in many important societal issues. Colloquia generate objective, independent, peer-reviewed reports that are made publicly available at no cost. Many of these reports explore how microbiology can contribute to solving important grand challenges, for example:

- Incorporating Microbial Processes into Climate Change Models (2011 forthcoming)
- Global Food Safety: Keeping Food Safe from Farm to Table (2010)
- Bioinformatics and Biodefense: Keys to Understanding Natural and Altered Pathogens (2009)
- Antibiotic Resistance: An Ecological Perspective on an Old Problem (2009)
- Clean Water: What is Acceptable Microbial Risk (2007)
- Microbial Energy Conversion (2006)
- Microbial Triggers of Chronic Human Illness (2005)

An important benefit of the colloquium format is that it provides a venue for microbiologists to meet with scientists from other disciplines, educators, administrators, public servants, engineers and others to consider challenges from many different perspectives, generate new ideas and devise common approaches. Such a format would be a fruitful way to address the questions posed in the Bioeconomy Blueprint RFI – each of which would benefit from collective brainstorming among many different constituencies. Relying on its more than 15 years of experience with this format, the ASM would be happy to aid the OSTP in convening groups who can further define the bioeconomy blueprint.

Respectfully submitted on behalf of the American Society for Microbiology

David Hooper, President of the American Society of Microbiology
Roberto Kolter, Chair of the ASM Public and Scientific Affairs Board
Bonnie Bassler, Chair of the Board of Governors, American Academy of Microbiology

PhRMA

December 6, 2011

VIA ELECTRONIC SUBMISSION

Ted Wackler
Deputy Chief of Staff
Office of Science and Technology Policy
Executive Office of the President
725 17th Street, Room 5228
Washington, DC 20502

RE: Request for Information: Building a 21st Century Bioeconomy

Dear Mr. Wackler:

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to respond to the Office of Science and Technology Policy's (OSTP's) Request for Information to inform the development of a robust bioeconomy. PhRMA represents the country's innovative pharmaceutical research and biotechnology companies, which lead the world in the pursuit of new, life-saving and life-enhancing medicines. Consistent with the Congressional Budget Office's finding that the pharmaceutical sector is one of the nation's most research-intensive sectors,[1] industry-wide investment in discovering and developing new medicines reached a record $67.4 billion in 2010. PhRMA members alone accounted for nearly $50 billion of this amount. Medicines developed by the sector have produced large improvements in health across a broad range of diseases, with the rapid growth of biological knowledge creating growing opportunities for continued profound advances against disease.[2]

Today, more than 3,000 medicines are in clinical trials or under review by the Food and Drug Administration (FDA) in the U.S. versus about 2,200 medicines in development for the rest of the world combined. The need for continued development of new treatments is as important as ever—for instance, the annual cost of Alzheimer's disease alone will increase from $183 billion in 2011 to $1.1 trillion in 2050 unless new treatments are found that delay its onset or slow its progression.[3]

U.S.-based biopharmaceutical research makes important economic contributions to U.S. gross domestic product, contributions likely to grow if the underpinnings for large-scale research and development (R&D) investment remain intact. A recent study[4] by the Battelle Technology

1 Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," 2006.

2 See, e.g., CASCADE Collaboration, "Determinants of Survival Following HIV-1 seroconversion after introduction of HAART," *The Lancet*, 362 (2003):1267-1274;. F. R. Lichtenberg, "The Expanding Pharmaceutical Arsenal in the War on Cancer," National Bureau of Economic Research Working Paper No. 10328 (Cambridge, MA: NBER, February 2004); Tufts Center for the Study of Drug Development, "Personalized Medicine Is Playing a Growing Role in Development Pipelines," Impact Report, 12 (Nov/Dec 2010): 6.

3 Alzheimer's Association, "2011 Alzheimer's Disease Facts and Figures: Use and Costs of Health Care, Long-Term Care and Hospice," 2011.

4 Battelle Technology Partnership Practice, "The U.S. Biopharmaceuticals Sector: Economic Contribution of the Nation," Battelle Memorial Institute, Prepared for the Pharmaceutical Research and Manufacturers of America, July 2011.

Partnership Practice reports that, the U.S. biopharmaceutical sector "is well recognized as a dynamic and innovative business sector generating high quality jobs and powering economic output and exports for the U.S. economy." According to Battelle, the U.S. biopharmaceutical sector supported a total of 4 million jobs in 2009, including nearly 675,000 direct jobs. Battelle also reports that the U.S. biopharmaceutical sector has a high multiplier effect--in 2009, each job in a biopharmaceutical research company supported almost five jobs across the economy, ranging from biopharmaceutical manufacturing jobs to construction and other building service jobs, to contract researchers and child care providers. Battelle found that across all occupations involved in the biopharmaceutical sector, the average wage is higher than across all other private sector industries, due to the sector's role as a "high value-added sector." In 2009, the average total compensation per direct biopharmaceutical employee was $118,690, compared to $64,278 in the overall economy.

These characteristics reinforce the importance of fostering an environment that will improve the private sector's ability to harness research innovations to meet national health challenges and continue to create high-wage, high-skill jobs. America's innovative biopharmaceutical companies face increasing challenges ranging from the cost and increased complexity of bringing new medicines to patients, the prospect of attracting and sustaining the capital needed to develop tomorrow's new treatments and cures, the increasing uncertainty related to coverage and reimbursement of innovative medicines, and intensifying competition from other countries. Continued innovation is fundamental to U.S. economic well-being. A long-term commitment to science, technology, and innovation is vital to enabling U.S. biopharmaceutical companies to improve health outcomes and establish the foundation for economic growth and jobs of the future.

Achieving growth in the bioeconomy that benefits all Americans calls for recognizing medical innovation as a valued part of the health care and economic solutions available to the United States, rather than as developments that should be suppressed. Medical advances are needed to help us innovate our way out of a myriad of systemic health system problems. Better treatments, which have yielded longer, healthier lives, are based on intensive R&D-- the lifeblood of the sector's economic value and growth. Because of their high added value, medical advances generate valuable jobs that help support vibrant communities across the country.

In order to create a more favorable environment for innovation, PhRMA believes the public and private sectors must work together to:

- Strengthen the science base to meet 21st century challenges;
- Advance medical innovation policies as a solution to health system problems;
- Sustain U.S. global leadership in the biosciences through economic trade, and related policies;
- Support strong intellectual property (IP) rights and enforcement in the U.S. and abroad; and
- Build a highly skilled and educated biosciences workforce.

PhRMA's comments are offered as a contribution to the national dialogue about how to spur innovation to address a broad range of health challenges, grow jobs, and strengthen the U.S. economy. As the bioeconomy blueprint and action plan are developed, it is critical that OSTP and other Federal agencies recognize the importance not just of identifying new ways to better

leverage public and private sector investments, but also of identifying and addressing challenges that increase the uncertainty for biopharmaceutical companies in the U.S. and restrict or reduce patient access to medical innovations.

Identification of Grand Challenges

It is laudable to seek to identify a limited number of "grand challenges" on which to focus public and private sector investment. There are unmet medical needs across a wide range of conditions and diseases that would be considered grand challenges. While recognizing these imperatives for sustaining biomedical advances, the RFI's "grand challenges" approach could inadvertently fail to recognize, and thereby disincentivize, the multiple paths needed to meet and overcome those challenges. At times, there are obvious paradigm-changing breakthroughs, quickly recognized as such. However, it is much more often the case that profound improvement in treatment and outcomes is the result of cumulative steps, no one of which is "the" breakthrough but the absence of any one of which could sever the route to advancements. Moreover, whether progress occurs through one breakthrough or through cumulative steps, typically, the full value of new treatments emerges over a period of time rather than at the time of product approval. Thus, a construct that would value only the rare and obvious paradigm-changing breakthroughs and discount other advances would cut off a common route to highly valuable advances and create very significant disincentives for innovation. As noted in a recent Boston Healthcare Associates white paper on progress against cancer, "Because of the nature of the research process, initial trial data alone cannot reflect the clinical value of a therapy earlier in treatment or disease state, across different diseases, in combination with the complete array of other therapies, or within target populations identified through specific biomarkers." [5]

Strengthen the science base to meet 21st century challenges

In this section we highlight two areas for consideration in the bioeconomy blueprint: the pending Prescription Drug User Fee Act-V (PDUFA-V) and public-private partnerships. A key focus of the bioeconomy blueprint must be efforts to advance regulatory science and to ensure that the FDA, National Institutes of Health (NIH), and related federal research agencies are sufficiently funded and remain up to date on the leading science and technological advances. In terms of reducing regulatory barriers which impede or prevent biomedical innovation, many of the topics within the purview of the FDA are to be addressed in the pending Prescription Drug User Fee Act-V (PDUFA-V), which is scheduled for reauthorization in 2013. The PDUFA-V agreement will, if enacted as published, continue to provide the FDA with resources and management tools to support patient safety and to promote innovation. Specific provisions that will enhance the FDA's reviewing capabilities include:

- An enhanced review model for new molecular entity new drug applications and biologics license applications to improve the efficiency and effectiveness of the regulatory review process for innovative medicines and biologics. This new model will also help avoid unnecessary delays in the availability of new treatments to patients for unmet medical needs, while still retaining FDA's high review standards. The enhanced review model allows for increased meaningful communication between FDA and sponsors prior to and

5 Chan, S, et al., "Recognizing Value in Oncology Innovation," White Paper, Boston Healthcare Associates, March 2010, Available at: http://www.bostonhealthcare.com/objects/PDFs/OncologyWhitePaper.pdf

throughout the regulatory review process and provides the FDA with management tools which emphasize completion of agency work within the first review cycle.

- Appropriate staffing and resources for the FDA that will advance regulatory science through the integration of emerging scientific data and innovative approaches to the development and review of new medicines more efficiently, promoting public health in areas such as biomarkers, pharmacogenomics and rare and orphan drug development.
- Enhancements to FDA's regulatory decision-making and transparency through the development of an organized, structured framework for evaluating the benefits and risk of new treatments in a consistent manner. The development and implementation of a patient-focused, structured framework will help ensure that FDA's regulatory decisions are based on the best available science and facilitate the balanced consideration of the benefits and risks of new medicines.
- Enhancement and modernization of the FDA drug safety system through a public process to help standardize risk evaluation and mitigation strategies, with the intent to assess and reduce burden on healthcare providers and patients, as well as the continued evaluation of the feasibility of using the agency's Sentinel Initiative to actively evaluate post-marketing drug safety issues.

The rapid pace of development and scientific advancement can make it difficult for the agency to stay current across all areas of science. Such advancements highlight the importance of ensuring the ability for both the private sector and regulators to have access to qualified external expertise.

PhRMA agrees there is a shared need and interest for both the private sector and FDA to interact with the best scientific thinking. This need should not be viewed as constituting an inherent conflict of interest. Existing conflict of interest rules that appear to only consider financial agreements between experts and companies without regard for scientifically legitimate involvement in research and product development activities may unnecessarily limit access to high-quality external scientific expertise. The present statutory and regulatory approach for resolving potential conflicts of interest significantly reduces any flexibility FDA has for gaining access to scientific expertise when experts have worked with biopharmaceutical companies on matters related to FDA's need for expert input. It is especially concerning that scientists and physicians who participate in clinical trials or provide expert scientific advice to companies may be prohibited from serving on relevant FDA advisory committees or in other roles where FDA has to rely on the best scientific and medical advice. PhRMA urges a careful examination of the FDA Advisory Committee process to ensure that FDA's access to needed scientific and technical expertise occurs in a more facile and timely manner. For example, a more consultative approach throughout the review and evaluation as scientific questions and issues are identified may render conflict of interest debates less important and provide the agency with more timely and useful scientific expertise. The FDA should also utilize scientific expertise in new ways by establishing "Centers of Excellence" for regulatory science where FDA can tap external resources to augment/enhance regulatory evaluative work.

Advance medical innovation policies as a solution to health system problems.

Biopharmaceutical innovation represents an important part of the solution to the health care challenges facing our nation. The continued discovery and development of new treatments saves and improves patient lives. It also produces savings through the avoidance of costly

hospitalizations and complications, increases in patient quality of life, and improvements in productivity.[6] As described above, major medical progress is often realized over time through a series of steps. Indeed, such "step-wise transformation" is frequently a fundamental characteristic of innovation. In addition, understanding of a medical advance's value frequently evolves over time and varies from patient to patient. To help realize the potential of medical innovation as a solution for improving patient outcomes and controlling rising health care costs, it is important to recognize across all policy areas that the full value of medical advances emerges over time and to support the ability of physicians and patients to choose from the full range of medically appropriate treatment options. The bioeconomy blueprint should also recognize personalized medicine and adoption of targeted therapies in medical practice. The emergence of personalized medicine illustrates how innovation is a solution, and underscores the importance of policy approaches that support physicians and patients in choosing from a range of treatment options to optimize care for the individual. For example, economists at the FDA estimated that the use of a genetic test to properly dose the blood thinner warfarin could prevent 17,000 strokes and 85,000 "serious bleeding events" each year and avoid as much as 43,000 visits to the emergency room.[7]

The need to control rising health care costs has been especially apparent during the recent economic downturn. Yet too often, approaches are pursued to control rising costs that, whether intended or not, thwart medical innovation and actually lead to higher future health care spending. In fact, many experts agree that medicines are a good investment in terms of lives saved, independence and productivity enhanced, hospital stays reduced, and surgeries and other costly, time-consuming procedures avoided. Likewise, continued development of new medicines is essential to avoiding the high burden of diseases such as Alzheimer's and Parkinson's diseases, diabetes, and mental illnesses.

Sustaining U.S. Global Leadership in the Biosciences through Economic, Trade, and Related Policies

Many countries have recognized the human and economic potential of the biopharmaceutical sector in the 21st Century and are seeking to build domestic industries. Among the approaches that the U.S. should consider are the following:

- Assess current federal policies that affect domestic R&D investments and access to global markets. For instance, the U.S. was one of the first nations to create an R&D tax credit, but has since fallen behind other nations.
- Review innovation strategies and economic blueprints developed by other countries to attract and grow the biopharmaceutical industry to identify potential effective policies and initiatives with implications for U.S. policy. As just one example, the U.K.'s Life Sciences Blueprint outlines a long-term strategy to enhance the U.K.'s global competitiveness in the biosciences.[8]

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6 See, e.g., Roebuck MC, et al. "Medication adherence leads to lower health care use and costs despite increased drug spending, *"Health*, 2011;30(1):91-9; McWilliams JM et al. "Implementation of Medicare Part D and nondrug medical spending for elderly adults with limited prior drug coverage." JAMA 2011; 27;306(4):402-9; Encinosa WE et al. "Does prescription drug adherence reduce hospitalizations and costs? The case of diabetes." *Advances in Health Economics and Health Services Research* 2010;22:151-73.

7 A. McWilliam, R, et al., "Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin," AEI-Brookings Joint Center, 2006, Available online at: http://aei-brookings.org/publications/abstract.php?pid=1127.

8 UK Office of Life Sciences, "Life Sciences Blueprint, HM Government," July 2009; Reuters, "Drug R&D projects win $330 mln from EU, industry," May 18, 2009.

- Assess the adequacy of existing trade, tax, and other public policies impacting the attractiveness of the U.S. as a preferred business location, particularly for R&D-intensive sectors like the biosciences.
- Strengthen and expand state and regional innovation clusters to include an explicit focus on sustaining and growing biosciences. Innovation clusters are critical incubators for innovation, resulting in faster improvement and innovation through competition and cooperation. This synergistic approach makes innovation clusters particularly strong contributors to the economy – through job creation and the rapid development of new technologies – and thus, an ideal target for public policies that promote their expansion.
- Enhance collaboration and build upon existing relationships with foreign regulatory agencies of similar standing. The U.S. should establish cooperation agreements between regulatory agencies of similar standing to eliminate unnecessary redundancies through coordination of activities, and mutual sharing and review of regulatory findings. This is not intended to undermine agency autonomy in regulatory decision-making but to encourage sharing of inspection and review tasks, particularly for applications intended for multiple markets.

Supporting Strong Intellectual Property Rights and Enforcement in the US and Abroad

To continue to foster economic growth and the discovery of medical breakthroughs, the nation must pursue public policies that advance innovation, and that requires the protection of intellectual property (IP) rights. Patents and data protection (also referred to as data exclusivity) provide a degree of certainty that biopharmaceutical companies and their investors will have an opportunity to recoup and secure the benefits of their significant investments. Weak IP protection thus has negative ramifications for both patients and workers here at home and abroad. Strong IP protections incentivize the R&D investment necessary to foster the discovery of innovative medicines that save countless lives around the world and lead to reductions in overall health care costs. Higher investments also support the creation of high-quality, high-wage jobs in the biopharmaceutical sector, boosting the U.S. economy. The U.S. biopharmaceutical sector's successes as well as its challenges highlight the importance of incentives that allow it to continue attracting the resources needed for a large-scale biomedical research enterprise that can deliver the medical advances society needs and desires. It is critical that an appropriate balance be struck between making room for additional competition and maintaining incentives for continued innovation. Patents and data protection, are both important incentives for innovation.

Patent protection and an effective patent system are critical to ensuring a favorable environment for R&D investment. At a time when we look toward the job growth the country needs, the Leahy-Smith America Invents Act has the potential to spur job growth by incentivizing investment in the patent-based businesses that provide millions of jobs across the country

To advance the discovery of new medicines, the data protection period, also referred to as a data exclusivity period, must be long enough to allow innovators, who undertake costly and risky R&D and the FDA approval process, to earn a positive rate of return. The Patient Protection and Affordable Care Act created an abbreviated approval pathway for biosimilars and provided for a 12-year period of data protection for innovator biologics. This provision allows innovative medicines to be on the market for a certain period before a biosimilar can be approved based on the innovator's data and protects against the uncertainties caused by patent challenges early in a product's life (but long after R&D investments are made).

In addition, the U.S. must continue to engage with trade partners on free trade agreements – like the Trans-Pacific Partnership – that foster and ensure strong IP rights, such as those found in the Korea-U.S. Free Trade Agreement and U.S. law. Greater emphasis should also be placed on enforcing trade rules to ensure U.S. trade partners meet their obligations, addressing preferential trade policies to improve the ability of U.S. companies to compete globally, and ensuring strong measures to combat counterfeiting. These efforts will ensure the U.S. biopharmaceutical sector's continued economic sustainability and growth.

Building a Highly Skilled and Educated Biosciences Workforce

Central to the Nation's ability to develop needed scientific and technological innovations is a highly skilled workforce. We need to nurture the development of workers in the fields of science, technology, engineering, and mathematics (STEM) for high-growth, high-value industries that are the most powerful engines of jobs growth. Worldwide trends indicate the U.S. is falling behind other countries in developing the educated and well-trained workforce necessary to compete globally and to meet the projected needs of biopharmaceutical companies in the U.S. As part of the bioeconomy blueprint, the U.S. should work to improve U.S. global STEM rankings through such efforts as improving coordination and accountability among federal STEM education programs and expanding federal support for graduate and early-career research in STEM fields. PhRMA also urges an increased emphasis on the biosciences in federal and state workforce training and retraining programs to ensure more Americans would be qualified to fill high-wage, high-quality jobs in the biosciences industry. The Bureau of Labor Statistics predicts 2.7 million STEM job openings in the U.S. by 2016, meaning that 2.7 million American jobs would be unable to be filled by American workers if current trends continue.[9]

In addition, just as other countries are implementing a range of incentives to attract and retain highly skilled workers, the U.S. should explore with the biopharmaceutical and related sectors ways to improve U.S. ability to grow a 21st century biosciences workforce, including attracting and retaining highly-skilled foreign workers.

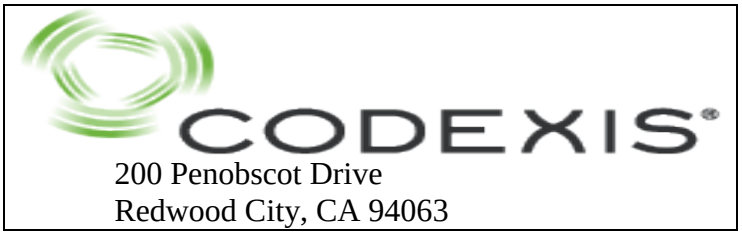
Ongoing commitment and engagement by both the public and private sectors is critical to addressing the challenges that exist and lay ahead as well as allowing us to collectively serve as sources of continued medical innovation and future economic growth. The increasingly challenging regulatory environment, the uncertainty related to whether innovation will be adequately valued by payers, the increasing complexities of the science and new technologies,

9 Dohm, A, and Shniper, L. "Employment Outlook 2006-2016: Occupational Employment Projections to 2016," U.S. Bureau of Labor Statistics, November, 2007, Available at: http://www.bls.gov/opub/mlr/2007/11/art5full.pdf.

and the uncertainties related to IP protections and the changing economics of industry underscore the need for a national strategy to strengthen the U.S. bioeconomy. We look forward to discussing these ideas and working with Federal agencies and other stakeholders to create a more favorable environment for medical innovation in the U.S.

Sincerely,

Richard I. Smith
Executive Vice President, Policy and Research



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Response to 10/11/11 OSTP Request for Information

Introduction to Codexis

Codexis, Inc. (Nasdaq: CDXS) is an industrial biotechnology company, based in Redwood City, California, focused on developing biocatalysts that make manufacturing processes faster, cleaner and cheaper. Today, Codexis has 300 employees worldwide. Codexis is a two-time recipient of the EPA Green Chemistry Award for manufacturing processes for the blockbuster drugs Atorvastatin and Sitagliptin.

Codexis' key technology encompasses optimization of individual enzymes as well as entire host strains using the CodeEvolver™ directed evolution technology and developing integrated processes with these biocatalysts. Codexis serves major worldwide markets where clean technology can make a positive economic and environmental impact. The Codexis CodeEvolver ™ directed evolution technology accelerates development of high value sustainable products. Our focus is on the cost-effective conversion of renewable resources into transportation fuels, pharmaceuticals and biobased chemicals, and on the development of new technologies for effective air (*e.g.*, carbon capture) and water treatment. Codexis is also developing fatty alcohols for the detergent alcohol market that can also be processed into renewable diesel and jet fuel. Accordingly, all of Codexis' answers to this RFI are focused on the biofuels and biochemicals sectors of the bioeconomy.

Codexis thanks the Office of Science and Technology Policy ("OSTP") for this opportunity to offer our input on building the 21st Bioeconomy. If there are any questions about our submitted responses, or if Codexis can otherwise be helpful to the OSTP as it works to develop a National Bioeconomy Blueprint, please contact Jacques Beaudry-Losique, Vice-President, Corporate Development & Strategy, (phone) [redacted], (email) [redacted]

Question 1. Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

Considering that the United States has already developed the most advanced biomass-based chemicals and products technologies in the world, our country is well-positioned to lead the global economy in the bioproducts sector. According to the Biotechnology Industry Organization ("BIO") in testimony to the Senate Committee on Banking, Housing, and Urban Affairs on December 1, 2011, there are 1.42 million Americans directly employed in the

biotechnology industry. BIO has explained that "[t]he biotechnology industry has long been an engine for economic development and job creation across the country and our sector is working to add more high-wage high-skilled jobs to our workforce." As part of the biotech sector, the biobased products industry offers ample untapped growth potential. Sustained government support for near-term petroleum displacement through non-fuel bioproducts could create tens of thousands more jobs and high-value, exportable intellectual property to help revitalize the U.S. chemicals and plastics industry.

The potential for biobased products to help reduce our dependency on oil as well as deliver a better environmental future must be harnessed through a long-term commitment by the public and private sector. Some key incentives and policies Codexis would encourage the Federal government to commit to include:

(a) Maintain a strong Renewable Fuels Standard, implemented with continued vigor by the EPA.
(b) USDA programs (BCAP, others) which support a predictable second generation feedstock price, not to exceed a contractual level of $70/ton to the biofuels facility owners/operators.
(c) Easier Access to DOE National Labs expertise to support technology based commercialization bottlenecks, through quick turnaround contracts and attractive rates, with strong IP protections for the users.
(d) Availability of financial instruments to fund commercialization through a semi-private commercialization and development bank, on the model that exists in many other countries in the world (Brazil: BNDES), or even in the US (Ex-Im bank) for other uses.
(e) 10-years off-take supply agreements from DOD or GSA for both demonstration (2 million gallons per year or equivalent) and for pioneer commercial plants 20 million gallons per year or equivalent).
(f) Extend the $1.00 cellulosic tax credit expiring on December 31st 2012 for at least 5 years, and preferably 10 years.

Question 2. Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

There are two types of innovation opportunities to develop the bioeconomy:

(1) "Vertical" opportunities in which the government invests in end-to-end technology pathways that can produce specific outcomes or products, such as an innovative biological pathway to produce a specific fuel or chemical molecule from biomass feedstock, for example. This applied research consistent with the roles of EERE (lower risk approaches) or ARPA-E (game changing breakthroughs)..

(2) "Horizontal" or fundamental opportunities, in which the government could invest in technologies that facilitate innovation across the board, such as better characterization tools for micro-structures or enzymes – or in improving our fundamental knowledge of chemical catalysts. This is more the focus of the Office of Sciences or NSF, but these programs are often disconnected from the business reality of the private sector.

In the case of industrial biotechnology, we believe that many of the major bottlenecks to growing the bio-economy at this point in time are in the realm of applied research. However, a more cost effective approach would be to focus on specific high risk elements within pathways as opposed to funding entire pathways. As GHG and food concerns mandate a quick evolution of the industrial toward second generation feedstock such as agricultural and forestry waste and energy crops, we believe that a useful focus would be on the following elements:

Biomass pretreatment: the energy intensive biomass pre-treatment process, which treats biomass feedstock to make it easier of access by enzymes, involves a high quantity of solids, and is poorly studied and understood. As a result, replicability and reproducibility of the process are not at acceptable levels, and this drives higher capital, energy, and enzyme usage costs. This important process step, critical to the feasibility of using second stage biomass, has not benefitted from smart, focused government funding. We need better biomass pre-treatment predictive performance tools as well as industry access to a variety of scale-up conditions. We recommend a 5-years biomass pretreatment program designed in collaboration with industry.

Focus on big, large scale petroleum derived chemicals: While the government focus in recent years has been on biofuels, we would like the government to consider investing in applied research to fund new biological pathways to produce major hydrocarbon based chemicals such as ethylene, acrylic acid and some of the twelve major biobased "platform" chemicals identified by DOE National Labs in the past decade[1]. Not only would this displace a substantial amount of fossil fuels, but it would also speed up commercialization of profitable biochemicals, minimizing the long-term need for government support programs. Since biofuels compete in a cost-driven, high volume commodity market, they require far more initial government support than higher value biochemicals to become economically sustainable. Developing the biochemicals industry will also develop a supply chain nearly identical to that of biofuels, thus enabling to meet public policy objectives (energy security, climate change) at a far lower cost. Government investment should also be focused on technology pathways with the most promising LCA profiles, based on a full accounting, and discard investments on more "LCA-marginal" technologies and processes.

Focus on deployment: As hundreds of industrial biotechnology companies have emerged over the past five years, developing dozens of potentially attractive technology pathways, the government should now focus in integrating these technologies into the marketplace. The government could play a huge role by using its purchasing power (DOD, GSA) to provide long-term biofuels and bio-products off-take agreements (10+ years) to industry suppliers, enabling these companies to access financing sources.

Question 3. What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

[1] Top Value Added Chemicals From Biomass, Produced by the Pacific Northwest National Laboratory (PNNL) and the National Renewable Energy Laboratory (NREL), 2004.

It is difficult to replicate biomass feedstock/pretreatment process combinations that deliver consistent substrates and compounds; thus, it is difficult to quickly validate our research approaches – because we are not getting reproducible results. Solids handling is also hard to scale and slows down our R&D throughput (see R&D recommendations in Question 2).

Another parameter that slows the scalability of second generation biomass is the presence of non-traditional sugars such as C5s. The C5 conversion rate is much slower than C6, because existing pathways are naturally C6 based. This prevents high performance, low cycle time end product production to occur, slows down scale-up efforts and drives higher capital costs.

Finally, the finishing steps of biofuels and bioproducts production require new product/impurities/water separation techniques which are complex, capital intensive and can reduce LCA benefits. This requires substantial applied research and engineering attention, and could also benefit from a 3-years DOE-industry research program.

Question 4. The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

Codexis does not agree with the premise of the question, with regard to industrial biotechnology, because sequence structure/function/production efforts are not the bottleneck to our commercialization efforts. We already have an excess of information to incorporate into our workflows. Codexis therefore recommends that what is needed is more multidisciplinary engineering-sciences collaboration to identify parameters need to be incorporated at lab level to ensure successful scale-ups.

Question 5. What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

Codexis will focus on answers on industrial biology products, as opposed to pharmaceuticals or biotechnology products, which face a very different set of scale-up and regulatory challenges.

- The first challenge for biofuels and biochemicals is their competition with legacy pathways from fossil fuels or natural oils, whose production costs do not reflect their negative externalities (greenhouse gases, health, deforestation, *etc*.).
- The second challenge is the cost of R&D, driven by expensive equipment, specialized labor and extended development timelines.
- The third challenge is the cost of scaling up and demonstrating the technology, which can run in the tens of millions of dollars. Furthermore, even a successful scale-up only gives a firm the "option" to build a first-of-its-kind, highly risky pioneer plant.

- The fourth challenge is the lack of commercial project financing for biobased pioneer plants, which require hundreds of millions of dollars of equity and debt. This problem is compounded for second generation plants (from biomass) that require a capital-intensive pre-treatment and enzymatic "front-end", which adds to the cost and the risk of the facility. The only option for U.S. companies is to tap foreign countries with capital intensive development banks and location subsidies, at the price of locating their facility in a foreign country. This is why we see much of the industry locating their first facilities in Brazil and in Southeast Asia, instead of the U.S.
- The fifth challenge is the lack of built-in infrastructure for the new industry, be it for feedstock, or with regard to the finished product, especially with regard to biofuels. Legacy industries control the downstream infrastructure physically and contractually, based on investments made over the past century.

Question 6. What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?

Not applicable to Codexis.

Question 7. What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

The Federal government could aggregate industry benchmark data on voluntary basis or on a mandatory basis (*e.g.*, with grant applicant or recipients). This would provide more performance transparency to the investment community as a whole. Such a list could include: feedstock type; conversion cost; enzyme cost; fermentation agent cost; LCA. The information would be sanitized so users could not determine the source of the information.

Question 8. What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

The two primary private sector models necessary to scale up promising bioeconomy firms are venture funding and project financing. While venture funding can bring an innovation to the verge of commercialization, it does not provide the capital resources needed to fund a first-of-its kind integrated biorefinery, which can cost in excess of $300 millions. Project financing is also a very difficult tool to apply, because it is premised on future cash flows, whose risks are mitigated by the presence of an off-take agreement for the product, a feedstock supply agreement, and a performance guarantee on the facility. Off-take agreements for fuels and chemicals do not have the terms length sufficient to support a long-term loan, and performance guarantees are impossible on "pioneer" plants because of the lack of historical statistical data on the technology performance.

The major steps that Codexis recommends that the agencies could take include:

- Use the government purchasing power to provide long-term off-take agreements (10+ years).
- Launch a quasi-governmental clean energy infrastructure bank with the authority to issue loans and loan guarantees to support the use of Project Financing.
- Protect the renewable Fuels Standards to ensure a government driven mandate to create market for biofuels.
- Look at developing a potential national labs role & expertise to validate new biofuels or product process technology and "certify" its potential performance. This information could be shared with prospective investors and lenders, but would not be available to the public at large.

Question 9. The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs

There is a huge scarcity of chemical and biochemical engineering graduates, and the government could help incentivize these disciplines by funding more internships. These internships would be very valuable as a preparation for private sector jobs. The government could also help foster more government-academic interactions.

Question 10. What roles should community colleges play in training the bioeconomy workforce of the future?

Industry could use more hands-on research associates from community colleges, with current training in biotechnology, fermentation and engineering. These resources are very hard to find for the private sector.

Question 11. What role should the private sector play in training future bioeconomy scientists and engineers?

The private sector needs to provide and invest in internal programs with discrete projects that could support a government sponsored internship program.

Question 12. What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

The national labs can encourage interactions between faculty, grad students and industry through creation of centers of excellence focused on bioenergy breakthroughs, such as the Joint BioEnergy Institute ("JBEI"). The JBEI is a San Francisco Bay Area scientific partnership led by Lawrence Berkeley National Laboratory. It includes the Berkeley and Davis campuses of the University of California, Sandia National Laboratories, the Carnegie Institution for Science, and Lawrence Livermore National Laboratory. JBEI's primary scientific mission is to advance the development of the next generation of biofuels — liquid fuels derived from the solar energy stored in plant biomass. See http://synbio.berkeley.edu/index.php?page=partners.

Question 13. What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation and b) could be reformed or streamlined while protecting public health, safety, and the environment.

In general, Codexis does not view regulations as a massive roadblock to bioinnovation. We believe that technology development and feedstock management or more critical path items pose the greater challenges. However, we provide the below list to demonstrate the kinds of regulations that impact Codexis bioinnovation activities and the implications of these regulations.

Clean Air Act RFS

Even though our biotechnology activities span beyond fuels to include chemicals and pharmaceuticals, we nevertheless believe that a strict interpretation of the RFS is the most important signal to investors that the Federal Government can provide. As a result, we support the strictest interpretation possible of the RFS within the language of the law. Furthermore, we believe that the RFS could benefit if it expanded from a strict focus on fuels production to a focus on the whole barrel of oil. For example, the production of chemicals from biomass that displace oil requirements are just as important for the nation's energy security and greenhouse gas emission balance than renewable fuels production. We believe that the RFS is a key tool to stimulate industrial biotechnology R&D activities, innovation and investment.

Clean Air Act Construction and Operating Permits

From an environmental permitting perspective, the critical path in permitting bio-refineries is the CLEAN AIR ACT Construction Permits. The federal government could show leadership and help the states by simplifying and expediting the review and approval of construction permits. This could be done without compromising air quality.

Codexis understands the requirements of New Source Review as a preconstruction permitting program. The applicable permitting requirements for Prevention of Significant Deterioration (PSD) requirements will depend on whether the proposed facility is a major or minor source and whether it is located in an attainment or nonattainment area. If the proposed facility is a major source, it will also require a Title V operating permit. We also understand that if our facility is in a Class I area, a Federal Land Manager (FLM) will have responsibility to review source impacts on site-specific air quality related values. Codexis also notes that in January, 2011, EPA announced that CO_2 emissions from biomass combusted at new and modified stationary sources will not trigger PSD permitting under the Clean Air Act for a period of at least three years. This has been made effective as of July 20th, 2011.

Clean Air Act New Source Performance Standards

It is important that EPA studies the impact of its New Source Performance standards on the permitting of biorefineries. Codexis understands that the New Source Performance Standards apply to new, modified, and reconstructed facilities in specific source categories identified by EPA that may apply to our downstream processing and finishing activities, such as hydro-treatment. A potential biorefinery, for example, would have to deal with permitting requirements for various components such as: Grain Elevator (Feed Handling); Stationary Gas Turbine; Small Industrial Steam Generator; Volatile Organic Liquids Storage; Sewage (Waste Water) Treatment; Petroleum Refinery, and VOC Emissions from Petroleum Refinery Wastewater Systems.

National Environmental Policy Act (NEPA)

Codexis understands that if a major federal action is involved in the siting of its proposed facility, NEPA requires that federal agencies have to assess the environmental consequences of their decisions before they undertake major federal actions that significantly affect the quality of the human environment. To help promote greater use of bioproducts, NEPA should be considered an integrated, expedited NEPA process to mitigate the financial and schedule risks to the applicants. Access to pre-permitted land on military or Federal Lands should be considered, as long as this does not add two or three years to the process, like the DOI Solar Programmatic EIS did with regard to Solar Concentrated Solar Power siting on Federal Lands.

Toxic Substances Control Act (TSCA)

TSCA regulates the manufacture and sale of chemicals. Of specific regulatory interest, Codexis uses genetically enhanced enzymes and organisms ("GMOs"), and may use feedstock derived from genetically modified seeds, approved for use in the United States. Codexis' plans for a first biorefinery project does not anticipate that such a project would have any changes to GMOs or other factors that would impact the ability to produce our bioindustrial products and/or biofuels at the projected volume and cost. Compliance with TSCA and other relevant requirements is a core component of Codexis' commercialization strategy.

EPA is considering reauthorization of TSCA. Although modernization of some of TSCA provisions are needed and generally recognized by industry and non-industry groups, these changes need to be done in a way that does not restrict innovation and does not compromise business confidentiality and intellectual property protection.

Energy Independence and Security Act (EISA), section 526

Section 526 requires that the life cycle green house gas ("GHG") emission of any fuel procured by the Federal government must be equal or below that of a conventional petroleum fuel. A lifecycle analysis ("LCA") of our green diesel fuel needs to be performed and compared to a baseline case of petroleum-based diesel. Codexis will use the GREET (Greenhouse Gases, Regulated Emissions, and Energy Use in Transportation) model that was developed at Argonne National Laboratory with support from the DOE's Office of Energy Efficiency and Renewable Energy.[2] There is still a lot of debate in the policy field on how to exactly do these LCAs and

[2] A very comparable study has been published by Argonne National Lab: ANL Report on Life-Cycle Analysis of Algal Lipid Fuels, August 2011. Download from http://greet.es.anl.gov/publication-algal_lipid_fuels.

make them comparable.[3] For instance, there are 13 studies on the LCA of fossil fuels and the GHG emission numbers that are reported in those studies differ by 30%. While we support the goals of Section 526, having more specific guidance from a government agency procuring fuel on how to address this issue in the response to a solicitation, and how the agency intends to evaluate responses in respect to compliance would be helpful.

Question14. What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

Please refer to Codexis' response in Question 13 for suggestions regarding regulations. In addition, Codexis strongly recommends that having well written clearly stated and transparent processes for protecting intellectual property and business confidential information are key in providing the confidence to justify the large private sector R & D investments in biotechnological research. Without these assurances, we put our existing stakeholders' investments at risk and put unnecessary constraints on our ability to attract future investors. No one, of course, argues with the need for regulations to protect human health and the environment. This industry is based on reducing environmental impacts. However, to stimulate and encourage investment, the regulations need to be written and implemented in a way that supports innovation and protects intellectual property. Federal agencies have the opportunity to lead the way in this area.

Question 15. What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

Codexis would respectfully suggest that Question 15 is not the right one and rather should be turned around to focus on the opportunities (vs. challenges) that new or emerging technologies represent to existing and proposed regulatory structures and the regulatory frameworks should be restructured to encourage these innovations. Existing regulations tend to be technology based on an emissions control approach. They are based on the assumption that there will be discharges to the environment and that adding controls at the end of the pipe is the way to reduce impacts to the environment. What if there was no "end of the pipes"? Regulations and the associated investment incentives could be written to encourage 'no discharge" technology and plant design. Regulations could also encourage biorefineries to be designed and built to produce multiple products such that the byproduct from one process in the raw materials for another, as opposed to strictly to penalize "discharges". Codexis suggest that there might be an opportunity for OSTP to work with regulatory agencies and convene stakeholders to "drill down" on potential new regulatory approaches.

[3]A description of LCA design is discussed in: AFRL-RZ-WP-TR-2009-2206 Advanced Propulsion Fuels Research and Development - Framework and Guidance for Estimating Greenhouse Gas Footprints of Aviation Fuels. Download from www.dtic.mil/dtic/tr/fulltext/u2/a513106.pdf.

Question 16. What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

The Federal government needs to substantially increase its funding of R&D, and without picking "winners' and "losers", provide funds, national labs facility access and expertise to solve the scientific and technology bottlenecks that prevent the large scale production of bio-derived fuels and chemicals. These bottlenecks could be either identified through a series of workshops organized jointly by DOE, OSTP and NSF, or through RFIs and/or solicitations that would request private industry to identify major research projects around these bottlenecks, which could then be sorted by an expert merit review panel. For example, biomass pretreatment, as identified in our response to Question 2, is a critical bottleneck that the government could help address.

The Federal government has the ability to play a key role on infrastructure development, especially with regard to using second generation feedstock or biomass. The embryonic second generation feedstock market suffers from the lack of farmers' appetite for risk taking in an era of high commodity prices, the lack of collection and harvest tools for agricultural residues and new energy crops, and the lack of critical infrastructure, such as widened bridges and wider roads that are needed to accommodate the movement of millions of tons of biomass to the future biorefineries. Furthermore, investment in additional rail cars, loading and unloading docks, and pipelines will be necessary to accommodate the new production that will in large part come for biomass intensive regions such as the Midwest agricultural areas, the Great Plains, and the Southeastern and Western forestry areas. Codexis recommends a series of workshop on these topics involving DOE, DOT, USDA and OSTP, as a start. Further discussion on the role of CRP land would also be important, and should include entrepreneurs, farmers, NGOs and the Federal Government, especially the USDA.

Question 17. What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

The industry supports the bioenergy center model funded by the DOE Office of Sciences, which work collaboratively through multidisciplinary partnerships to bring about new biobased products, methods and tools that the industry can use and other precompetitive elements of research. DOE established three Bioenergy Research Centers ("BRCs") in September 2007. The three centers are:

- DOE BioEnergy Science Center ("BESC") led by DOE's Oak Ridge National Laboratory in Oak Ridge, Tennessee.
- DOE Great Lakes Bioenergy Research Center ("GLBRC") led by the University of Wisconsin in Madison, Wisconsin, in close collaboration with Michigan State University in East Lansing, Michigan.

- DOE Joint BioEnergy Institute ("JBEI") led by DOE's Lawrence Berkeley National Laboratory.

Codexis highly recommends that these three bioenergy centers (JBEI, BESC and GLBRC) continue to be funded so that they can continue to inspire, support, and guide the biotechnology revolution.

Proposal for the Bioeconomy Blueprint **December 6, 2011**

Division of Foodborne, Waterborne and Environmental Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

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Executive Summary

Safer Food and Improved Patient Diagnosis through an Advanced Nation-wide Genomic-based Enteric Disease Detection and Investigation Network. Foodborne disease is a large, costly, and under-recognized health challenge, but one that has the potential to be significantly addressed by biotechnological innovation. PulseNet and the Nation's foodborne disease surveillance system have been among the most successful new drivers of food safety in a generation, and play a pivotal role in our increasingly globalized food production and distribution system. Current successes likely represent only a small fraction of the true potential of these networks. This system depends on the nation's clinical laboratories for samples from ill individuals, which are compared by "DNA fingerprinting" techniques to find patterns of disease that may signify an unrecognized problem in our food or water supplies. However, new clinical diagnostic technology is being introduced which will make private and commercial testing activities incompatible with public sector disease-tracking, thus threatening our ability to detect and respond to outbreaks. Development of next-generation genomic and metagenomic technologies and analytic capacity will give the nation an opportunity to sync private sector and public health disease detection efforts, improve the predictive value of diagnostics, and will likely allow the nation's food safety system to more fully exploit the rich resource that foodborne disease surveillance represents. Furthermore, software and hardware developed to address this issue, coupled with publicly-available data from a large-scale metagenomic infrastructure will leverage development across a range of biotechnology, pharmaceutical and diagnostic manufacturers.

1) **Grand Challenge:** Safer Food and Improved Patient Diagnosis through an Advanced Nation-wide Metagenomic-based Enteric Disease Detection and Investigation Network

Background

National foodborne disease tracking networks have a large impact on disease: Each year approximately 48,000,000 people in the U.S., or 1 in 6 Americans, contract a foodborne disease, 128,000 are hospitalized and 3,000 die. Unlike many other conditions, foodborne

disease is largely preventable, and for that reason has been designated as a "winnable battle" by the CDC. Disease surveillance has proven to be one of the most robust mechanisms available for detecting problems in the food and water supplies that are not recognized through the normal regulatory processes, and one of the most straightforward and cost-effective means of improving food safety. New tools, such as PulseNet, have significantly improved our ability to address the problem.

PulseNet, the nation's molecular subtyping network for enteric disease, has played a key role in virtually every high-profile foodborne disease reported in the national media since its inception in 1996. PulseNet obtains a "DNA fingerprint" from pathogens isolated from individual patients and matches the fingerprints to detect local, national, or international clusters of disease that may represent wide-spread outbreaks. It is comprised of 87 federal, state, and local laboratories in the U.S., and 82 countries around the world. Together with OutbreakNet, the national network of state and local officials who investigate foodborne outbreaks, over one half billion pounds of contaminated food have been recalled from the U.S. marketplace in PulseNet's first 15 years. More importantly, PulseNet-triggered investigations have stimulated improved safety practices in a wide range of food industries, such as the beef, poultry, shell egg, ready-to-eat meat and prepared meal, leafy green and vine vegetable, sprout, melon, flour, spice, tree nut, and peanut industries. In addition to prompting self-improvement by industry, these investigations have provided FDA and USDA the information they need to focus their activities on the products most likely to cause disease, both in domestic and imported products. Outbreaks can now be detected more quickly than ever before, making it less likely that American's will experience the type of widespread *E. coli* outbreak that devastated Germany and the rest of Europe in 2011. While it may seem counter intuitive, improved outbreak detection and investigation improves confidence in U.S. industries in the long run, and improves the quality-of-life for every American.

Need for new technology:

The current National Foodborne Outbreak Detection System is not in sync with private development, which threatens our Country's ability to rapidly detect food-related outbreaks: The ultimate source of all information for foodborne disease surveillance is obtained from diagnostic testing and exposure assessment of ill patients. A new generation diagnostic testing that does not depend on culture and isolation of pathogenic bacteria is being developed by the private sector at a rapid pace, with several kits already in the medical device approval pipeline. While these "non-culture" tests may improve service to individual patients, they do not provide the isolates which are needed for public health surveillance programs such as PulseNet. Furthermore, some non-culture tests require specimens that are incompatible with culture, making reflex culture (culture of positive specimens) impossible. This deficit will weaken critical foodborne disease surveillance programs that depend on

isolates, including PulseNet, OutbreakNet, FoodCORE, the Foodborne Diseases Active Surveillance Network (FoodNet) and the National Antimicrobial Resistance Monitoring System (NARMS), which will result in vulnerabilities and gaps in the food safety system. Programs at FDA and USDA which depend on CDC data will also be negatively affected, such as FDA CORE, and the USDA's predictive analytics program. If diagnostic development eventually moves to completely preclude primary culture, major unintended consequences could include hundreds of thousands of unnecessary illnesses resulting from the inability of our surveillance systems to rapidly and reliably detect outbreaks, and reduced information needed for industry to produce safe food. New "culture-independent" molecular strain typing and characterization methods need to be developed for the public sector that are compatible with, or complement, tests developed in the private sector so that the needs of both patients and the general public are met.

Foodborne disease surveillance system has vast largely untapped potential: As successful as our foodborne disease surveillance and investigation programs have been, they are likely operating at only a small fraction of their true potential. A relatively small percentage of PulseNet clusters are solved in most states, leading to a loss of many prevention opportunities.. The basic elements needed to make the system more effective both for patients and for the general public are well known. They involve getting better and faster information about what made individual cases sick, and more effectively detecting and investigating identified clusters of disease.

The current system relies on many steps that occur in a more-or-less sequential manner, from the patient presenting to their physician; the physician ordering a test; reporting of the positive test result to public health authorities; shipping the isolate to a public health laboratory; performing molecular subtyping tests; uploading of "DNA fingerprints" to local and national databases; detecting and investigating clusters of illness; interviewing patients for food and other exposures; and finally follow-up by health, regulatory, and industry partners. The longer the process takes, the lower the probability that the investigations will be successful because patients quickly forget their activities and what they ate, contaminated foods may be completely consumed or disposed of by the time they are identified as a probable vehicle, and the trail of investigation clues quickly grows cold.

PulseNet addresses a small but important fraction of foodborne disease cases. Currently tracked microorganisms represent less than three percent of all foodborne disease infections, meaning that approximately ninety-seven percent of this valuable information remains to be exploited. Over eighty percent of infections are thought to be due to unknown etiologic agents. Identifying the bacteria, viruses, and parasites that are currently unknown but nevertheless making individuals sick is a particularly productive means toward devising new prevention strategies.

The solutions to making the system dramatically more effective are technological (e.g. getting molecular epidemiology information closer to patient diagnosis) and process-dependent (e.g. obtaining high-quality standardized exposure information). These needs were recognized in the "FDA Food Safety Modernization Act of 2010" (S 510) and the "Improving Food-borne Illness Surveillance and Response Act of 2008" (S. 3358).

Harnessing advanced biological technology to meet the challenge

Genomic methods: Whole microbial genomes can now be sequenced in days or hours, instead of weeks or months that were required just a few years ago. Bioinformatic analysis is now the rate-limiting step (see "critical challenges" below). Currently, the most effective means of sequencing is by the use of microbial "isolates." Genomic data can be used for:

(1) Tracking microbes in the population. Any level or multiple levels of strain resolution needed for outbreak detection or investigation can be generated with whole genome sequence data. Genomic methods may be backwards compatible with current methods through the use of *in silico* analyses. If done rapidly, the routine use of genomic data to compare human disease with environmental, food, and animal testing can help quickly identify what foods or other exposures are making people ill, without many of the limitations of current fragment-based molecular surveillance techniques.

(2) Identifying new targets for next-generation PulseNet methods, which will allow the identification of specific microbial strains and important virulence factors in complex samples, such as human stool. When combined with industry-developed platforms, this has the potential of revolutionizing the commercial diagnostic market.

Metagenomic methods: It is now theoretically possible to sequence all members of a microbial community, such as human stool. This is currently the "holy grail" of enteric diagnostics. Unlike the" holy grail", building national capacity to make metagenomics a routine diagnostic and public health tool is an attainable goal. However, it is not yet practical to analyze metagenomics data in a timely manner (see "critical challenges" below).

Application of genomic and metagenomics sequencing methods: These methods have the potential to:

- Rapidly identify any known microbial pathogen, or combination of pathogens. This "Star-Trek" type technology was only science fiction only a few years ago, but is rapidly becoming technically feasible. Preliminary data suggests that many enteric illnesses are due to combinations of pathogens, or pathogens in the presence of other bacteria or specific virulence factors. There is currently no practical way to identify these effects, either for patient diagnosis or public health action.

- Produce sequences for unknown microbial pathogens in any patient specimen, which can be linked and evaluated through outbreak investigations or large sporadic case control studies
- Preserve and improve PulseNet, OutbreakNet, FoodCORE, and our National Foodborne Disease Surveillance System. Bringing microbial strain tracking closer to the ill patient has the potential to greatly improve the speed and effectiveness of outbreak detection and investigation, especially when coupled with electronic cluster detection and national standardized exposure assessments. The improved resolution of sequencing compared to current subtyping methods will also enable us to identify microbial pathogens associated with particular food commodities and thereby to predict which food commodities are associated with sporadic foodborne illness (attribution). This information may also be used to target food safety intervention at the production level
- Identify food consumed by ill individuals. This may be very useful for illness with short incubation times, such as foodborne intoxications or toxin-mediated infections
- Identify microbial factors that contribute to the development of disease.
- Identify host factors contributing to disease.
- Increase the precision of strain assignments.

2) High impact research, innovative opportunities, and Federal priorities

a. **Direct impact:** For the same reasons that foodborne disease has been designated as a "winnable battle" by the CDC, this research will likely have a relatively rapid impact on a very large problem. An estimate by the Pew Trust places the total cost of foodborne disease to the U.S. economy at $152 billion dollars per year, with a high proportion of expenditures required for healthcare. As described above, foodborne disease is largely preventable, but prevention requires that we better understand the reasons causing 48,000,000 Americans to become sick each year. Improved outbreak detection represents one of our best opportunities for reducing the burden of disease by stimulating change in industry and focusing regulatory activities. It also is expected to reduce impact of outbreaks on industry, as advanced technology and epidemiology should reduce the time needed to identify single farms or producers responsible for contaminated products, thus protecting safe producers of the same commodity.

b. **Broad application:** Stool represents one of the most complex possible matrices, with over 10^{11} microorganisms/ml and more than 500 microbial species. PulseNet currently requires 50,000 – 60,000 analyses per year. Extending metagenomics to clinical diagnostics would be orders of magnitude more extensive. Development of the data pipeline and analytical tools needed to conduct large-scale metagenomics analyses is a bit akin to development of space technology. The tools needed to complete the task are broadly applicable to other national priorities

c. **International competitiveness:** A number of foreign countries including Canada and Denmark have made significant investment in bioinformatics infrastructure, at least in part to address enteric disease issues. Bioinformatics appears to be the rate-limiting step in the next phase of biotechnology development.

3) **Technical challenges**

a. Genomic sequencing technology development for metagenomics: In current sequencing technologies all DNA in a sample is sequenced in small bits and then assembled using specialized software. However, many genomic targets are present outside the chromosome, e.g., on extrachromosomal elements like plasmids, or are found in many different bacteria, both pathogens and commensals. Such targets may encode important virulence factors and antimicrobial resistance. In order to use metagenomics analysis for diagnostic and surveillance purposes it is critical to know exactly to which organism such genomic targets belong. It is therefore critical to develop high throughput technology to sequence all diverse members of the microbial population in a complex sample, e.g., stool, on cell at a time to ensure that all sequencing information from potential pathogens are captured reliably.

b. **Computing hardware, data pipeline, and software:** A whole genome sequence of a stool pathogen may contain 4,000,000 – 6,000,000 DNA base pairs. Depending on the sequencing assay, a single metagenomic analysis of stool may involve 500 times as much information. If one factors in depth of coverage, the data burden is more than an order of magnitude higher. Currently, analysis of a single stool sample can take weeks or months, and requires dedicated, high performance computing equipment that is not widely available. Even the networking infrastructure for transferring such large volumes of data within and between institutions is inadequate, and the available software is still under active development and not amenable to routine use.

c. **Research priorities to address challenges: Since our experience with whole genome and metagenomic sequence analysis is relatively new, it is still largely necessary to manipulate huge amounts of data to identify the information of interest.** Research involving industry, academia, and government could focus on streamlining analytical algorithms to reduce the amount of data that must be manipulated. Considerable research will be required to interpret metagenomic data. It will be necessary to examine known and unknown pathogens and pathogen combinations as epidemiological risk factors for disease, and to develop strategies to discount or discard data from organisms that are likely to be part of normal stool flora.

d. **Simple, concrete goals:**

i. **Next-generation PulseNet method**: Development of a new method for detecting and high-resolution characterizing single pathogens such as

Salmonella spp, Shiga toxin-producing *E. coli*, and *Listeria monocytogenes* directly from a clinical stool sample in one day for $50.

ii. **Stool metagenomics:** Stool metagenomic analysis in one day for $100. While ambitious, this is achievable in a few years if advances continue at their current pace, and if bioinformatics deficits are addressed.

4) **Prediction of gene product function through genomics:** Virulence factors for most bacteria are poorly understood, which makes for diagnostic and regulatory uncertainty. For example, the USDA has a zero tolerance for *Listeria monocytogenes* in ready-to-eat meats, but it not clear that all *Listeria spp* identified as *L. monocytogenes* are equally dangerous. Similarly, Shiga-toxin producing *E. coli* (STEC) are a diverse group of organisms found frequently in cattle and beef, but STECs are not equally likely to produce disease. Identification of additional virulence factors and their coding regions will be facilitated by analysis of large numbers of genomes coupled with epidemiological and medical information gathered through routine surveillance activities.
5) **Barriers preventing discoveries from moving from the lab to commercial markets:** The most effective surveillance system is one where analysis occurs as close to patient diagnosis as possible. That necessitates collaboration with private industry, which has primary responsibility for diagnostic test development. Components of an advanced analytical platform will need to be produced by private industry. Barriers should be minimal.
6) **Changes to SBIR and STTR programs required for accelerated commercialization:** not addressed in this document.
7) **High value data:** Large databases of genomic and metagenomic data will be an invaluable resource for commercial development. Currently, plans are underway to make all genomic data from enteric bacteria accessible to interested entities. Software developed as part of government-funded research will model development for applications in the private sector.
8) **Challenges with existing private-sector models**: Despite its importance, foodborne disease surveillance is a small market for commercial development, which has been a contributing factor to other data handling issues in the public sector. Furthermore, testing is not reimbursable as it benefits the general public but not the individual patient whose sample is tested. Development of metagenomic tools and capacity is a large project without immediate prospects of financial reward. As with NASA activities, commercial spin-offs utilizing traditional models should be plentiful.

9 - 17 Not applicable to this RFI

Comments Submitted by Randolph W. Hall
Vice President, Research, University of Southern California

Q1: Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

Grand Challenge 1: Access to Quality Affordable Health Care

The United States has by far the most expensive health care system in the world while delivering outcomes that are well below the best. Without intervention, the cost of health care is also likely to increase as populations age over the coming decades. **The grand challenge is to reduce health care costs to no more than 12% of the gross domestic product, while increasing average life expectancy to at least 82 years, by the year 2025.**

To address this challenge, research is needed on the following topics:

Health Economics and Policy: creating the incentive structure for the efficient delivery of health care, so that providers and insurers are motivated to eliminate waste that occurs due to: (1) care that is unlikely to provide substantial benefits to the patient, (2) resources that are under-utilized, (3) inappropriate use of expensive resources when cheaper alternatives exist, (4) delays in the introduction of new cost-effective therapies caused by regulatory burden.

Health Informatics: improving the use of informatics to assess the therapeutic approaches that are best suited to each individual, based on his or her health care history, genetic factors and biomarkers, health behavior and environment and proven efficacy of alternative approaches. Informatics should be used to provide a health care assistant to the provider and the patient to help them navigate through alternative therapies and make the best choices.

Health Care Efficiency: creating mechanisms to improve productivity, offering the capacity to serve more patients in less time while improving health outcomes. This can include methodologies to mine and analyze data sets to provide meaningful performance metrics in real time, and for retrospective analysis, and to couple efficiency methods to compensation and reimbursement.

Health Communication: developing tools to effectively share information with patients in a way that motivates them to make the best health care decisions and to prevent disease based on their circumstances. Likewise, developing tools to effectively share information with health care professionals and guide their decision should also be a priority.

Grand Challenge 2: Targeted Therapies and Diagnostics for Cancer

41% of Americans born today will be diagnosed with cancer at some time in their life. Nearly 600,000 people will die this year from cancer in the United States. Cancer is the second leading global killer, accounting for 12% of all deaths, and the World Health Organization estimates that

cancer will become the leading cause of death worldwide, as it already is in the United States. Despite the large investments in cancer research made in the U.S. over the last 50 years, we do not yet have the types of therapies and diagnostics that will dramatically alter cancer survival rates. **The grand challenge is to extend life expectancy by increasing the five-year survival rate among all malignancies to 90% by the year 2025, through innovative science-based therapies and diagnostics.**

The specific opportunity is to use nanomedicine and other techniques arising from chemistry and physics to precisely target therapies to disrupt the mechanisms by which malignant cells reproduce. Specific focus areas include:

Theranostics that use multifunctional nanoparticles to image the tumor, provide targeted treatment and assess in real-time the therapeutic action.

External activation of nanoparticles as a mechanism for non-invasive local delivery of drug and/or tumor ablation.

Nanoparticles, including their synthesis, genetic engineering, surface engineering and characterization that can be readily tailored for multifunctionality toward specific clinical applications.

Biomarkers that can be exploited to attach nanoparticles to specific cancer cells. Nanoparticle delivery of DNA/RNA based therapies.

These approaches can be integrated with modeling, simulation and information technologies, so that we can better predict, and precisely target, therapies and diagnostics.

Grand Challenge 3: Healthy Environments

Worldwide, nearly two million people (many children, who would otherwise live much longer lives) die each year due to unsafe drinking water and poor sanitation or hygiene. Close to one million people die each year due to exposure to unhealthy air. These and other environmental factors cause a huge loss of life around the world, particularly in developing countries where the life expectancy can be as low as 40 years. **The grand challenge is to increase the life expectancy of all countries in the world to at least 60 years through the improvement of environmental conditions and the prevention of disease.**

The approach should be to create an integrated program that merges public health with engineering to understand the causation of disease, simultaneously developing affordable technologies to remedy environmental conditions and understanding the cultural factors that may favor one solution over another. The United States should become the world leader in innovative technologies to improve water cleanliness, reduce emissions, and remedy other environmental hazards.

Q2: Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

Priorities should include research structured around these principles:

- Creation of new informatic tools for the storage, sharing, visualization and analysis of large biological data sets. These tools should be built on a platform of technology that includes high performance computing, high-speed networking and mobile devices. Advanced informatics should be used throughout all research in the bioeconomy.
- Encouragement of "open science" models of research, whereby data sets and other research products are freely shared among research communities.
- Collaborative science, whereby emphasis is placed on the creation of centers of excellence that bring together researchers, patients, students and industry within integrated environments, along the lines of NSF's Science and Technology Centers and Engineering System Centers.
- Completion of fundamental research that is informed by real problems.

Q3: What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

The critical technical challenge needed to advance high throughput approaches will be the management, sharing, integration and analysis of greatly expanded data sets originating from these technology. Research on the science of **informatics enabled discovery** should be the highest priority. Programs of research should focus on the creations of systems that allow for the expedited analysis of massive new data sets, and the presentation of results directly and immediately to the health care provider or researcher.

Q9: The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

The pathway to an academic career in the life sciences, combining doctoral and post-doctoral training, has become much too long and much too unpredictable. The NIH should consider limiting support for post-doctoral training for each recipient to no more than two years, and reinvesting the savings in support of additional research projects through other award mechanisms, such as the RO1. In addition, greater emphasis should be placed on the creation of professional education at the masters degree level. Seed funding for the creation of professional masters degrees should be a priority.

Q11: What role should the private sector play in training future bioeconomy scientists and engineers?

Private research universities play a critical role in the education of scientists and engineers. The University of Southern California alone awards more than 10,000 degrees each year, including more than 6,000 advanced degrees. It is critical for the federal government to continue supporting the research and educational endeavors of private research universities.

In addition, the private companies can contribute more in the future through the creation of internships and through cooperation in the dissertation portion of doctoral education. Support for industry research experiences whereby students would spend periods from 6 to 18 months at an industrial laboratory while completing their dissertations would be highly valuable. This might be enabled through grant supplements.

Q13: What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

The recently enacted rules on Responsibility of Applicants for Promoting Objectivity in Research will be a major burden on universities and likely impede progress in the bioeconomy. The direct cost of this regulation will exceed $1.5 million at our university over the next five years, not including the time burden imposed on investigators in the disclosure process. The regulation creates a new burden on universities to assess the relevance of investigators' financial interests to their research. The regulation will add to the length of time required to submit proposals to the NIH, and will inhibit investigators from participation in HHS due to the added regulatory burden associated with HHS funding. At the same time, the regulations do not address the most critical issue in conflict of interest: that of biomedical companies providing personal payments to investigators who simultaneously act as evaluators of biomedical products and promoters of the very same products.

In addition, with so many Federal funding opportunities requiring collaboration between multiple partners, sub-recipient regulations can be streamlined to reduce burdens and allow research teams to get to the research, rather than spend time and resources on paperwork. Regulations should be aimed at making collaborations easier to execute.

Last, the added reporting requirements associated with ARRA funding have been costly to our university. A reduction in such regulations would be beneficial.

Q16: What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

The bioeconomy lacks the agility of the software, computer and communication industries. The time to market is far slower, and the competitive pressures are much smaller. The highest

priority should be to make the bioeconomy more entrepreneurial and competitive by streamlining the regulatory process underlying

Q17: What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

It would be beneficial to create a DARPA-like model for advanced research in the life sciences. Through this approach, program officers would be empowered to build research communities to formulate new solicitations, and would have expedited mechanism to select proposals that are particularly innovative. The current NIH model that separates scientific review from the scientific programs inhibits the ability of NIH to implement creative research programs.

(1) $2 per pound domestically produced seafood; A Grand Challenge for the 21st Century Bioeconomy in the areas of health, the environment, and agriculture:

When is the last time you bought seafood in the grocery store? Where did it come from? How much did it cost?

Although the health benefits of a diet high in seafood are well known, American consumers continue to eat far less seafood than other forms of meat. This year new dietary guidelines (published by the U.S. Department of Agriculture and U.S. Department of Health and Human Services) call for Americans to double their seafood consumption. However, even at current levels of consumption, the U.S. produces very little of its own seafood supply and other forms of meat are available to consumers at much lower prices. This is not due to any inherent inefficiency in seafood production. Seafood can be produced in low energy culture systems and cultured seafood species normally have more favorable feed conversion ratios than terrestrial species. The lack of affordable domestic product is due to the relatively new and underdeveloped nature of the domestic industry.

Looking forward, finite wild seafood stocks combined with increased domestic and global demand (fueled by both population growth and increased per capita consumption) is likely to result in even higher prices and less availability of quality seafood for the U.S. consumer.

On a global scale, the shortage of wild seafood has been met by explosive growth in the agricultural production of aquatic organisms – herein referred to as aquaculture. Commercial aquaculture production currently makes up greater than half of the global seafood supply. However, the United States has lagged behind other nations in the development of this emerging form of agriculture. U.S. consumers have access to quality, safe, and affordable sources of red meat and poultry, raised in the U.S., under U.S. food safety and environmental regulations, yet only 5% of the seafood consumed in the U.S. is a product of domestic aquaculture. The U.S. represents one of the world's largest seafood markets (second only to Japan), but 86% of that market is supplied by imports, approximately half of which are foreign aquaculture products, contributing to a national seafood trade deficit which recently surpassed $10 billion per year.

Aside from issues of availability and price, U.S. consumers may avoid seafood due to concerns regarding the source, safety, and sustainability of seafood products. Although most of the seafood available to U.S. consumers is safe, there are valid concerns associated with seafood that has been harvested or farmed under less than adequate regulatory oversight. Such concerns would be addressed by the domestic production of seafood, under U.S. environmental and food safety oversight.

Any plan for building a 21st Century Bioeconomy should include the development of a sustainable domestic aquaculture industry that will be large enough to reduce the nation's seafood deficit, add jobs to the U.S. economy, and provide consumers with a quality, safe, and affordable supply of healthful seafood.

In 1980, the passage of the National Aquaculture Act made it this nation's policy to support the development of domestic aquaculture. However, 31 years after the passage of the act, the U.S. has made important contributions to aquaculture innovation, technology, and environmental management; but has failed to take a leading role in production. A modest domestic aquaculture industry has emerged, but not on a scale that can successfully compete with the lower cost of foreign production.

The U.S. demand for seafood is likely to continue to grow, and it is in the best interest of public health and the national economy to produce a greater proportion of that seafood domestically as part of the emerging 21st Century Bioeconomy.

A large scale domestic aquaculture industry will provide the following benefits:

- Benefits to the American consumer – Nutritious and affordable seafood. Clear understanding of the source, security, quality, and safety of U.S. farm-raised seafood.

- Benefits to the U.S. economy – A domestic aquaculture industry on the scale of other meat production industries in the U.S. would provide thousands of jobs in production, support, and scientific discovery. Such development would also be consistent with the objectives of the White House Rural Council to strengthen rural communities and promote economic development [http://www.whitehouse.gov/administration/eop/rural-council]

- Benefits to the environment – One of the world's largest seafood markets would become significantly less dependent on faltering wild fish stocks and on under-regulated foreign aquaculture. Additionally, many forms of aquaculture produce positive ecosystem effects (e.g., Oyster culture can restore degraded habitat and remove excess nutrients from the water column). Furthermore, a successful, competitive U.S. aquaculture industry would set the best practices standards for the rest of the world to follow.

Many of the funding sources that currently support domestic aquaculture development have been, or are likely to be, dramatically reduced in the current budgetary climate. The development of a large scale, competitive aquaculture industry in the U.S. will require commitment and decisive action by the Federal government, companies, academic institutions, non-profit organizations, and others, in the following specific areas:

Seafood species selection and development: The animals used in terrestrial agriculture today have undergone centuries of selective breeding, making them more efficient and productive. Because large-scale aquaculture is a relatively recent form of agriculture, there is still the opportunity to select and develop the most appropriate species for culture. Federal research in the area of selective breeding should be funded at higher levels because genetic improvement of aquaculture species has the potential to dramatically increase productivity, and there are few commercial operations that have the resources to maintain a selective breeding program.

Feed research: Feed comprises a large portion of production cost for any animal species. The same is true for aquatic species. Currently aquatic animal feed relies heavily on fish meal, harvested from wild fish populations, as a key feed ingredient. Since the amount of fish meal available from the wild is a finite and is dependent on fluctuations associated with wild populations, the cost of fish meal is a potential limiting factor for aquaculture production. Additionally, if increased aquaculture is to realize its potential to reduce pressure on faltering wild stocks of fish, alternatives to fish meal need to be developed for use in aquatic animal feeds. Terrestrial plants such as soybeans have shown promise as a partial replacement for fish meal, especially for some species of fish. Perhaps even more promising is the use of aquatic algae – the natural source of fish nutrition, in synergy with biofuel production. Every new feed ingredient needs to be approved by the Food and Drug Administration. The process for this approval requires substantial resources that are often beyond what is practical to spend on an approval for the relatively small U.S. aquaculture feeds market. Federal research should be focused on identifying, testing, and approving fish meal replacements for aquaculture feeds. The National Oceanographic and Atmospheric Administration and U.S. Department of Agriculture recently produced a draft document that outlines potential steps to address this issue. [http://aquaculture.noaa.gov/news/feeds.html]

Aquatic Animal Health: Aside from feed, another major cost associated with intensive animal production is the prevention and cure of infectious disease. Because aquatic animal husbandry is relatively new when compared to traditional agriculture, there is still a lot to learn with regard to aquatic disease agents and host species biology that might impact the productivity of domestic aquaculture. Developing the necessary diagnostic tools, drugs, and vaccines is an expensive proposition that is not justified by the current size of the U.S. industry. Federal effort should focus on developing the tools, knowledge base, and infrastructure needed to monitor, mitigate, treat, and control aquatic animal diseases.

Regulations: Adequate regulation of domestic aquaculture is critically important. A domestic industry would be of little value if consumers can not be certain that the product is of high quality and was produced in a manner that is safe for human consumption and for the environment. In many cases inefficient, confusing, overlapping, and/or undeveloped regulations are a hindrance to the expansion of U.S. aquaculture. The Federal government should make it a priority to critically evaluate its regulations regarding aquaculture, and address regulatory inefficiencies. States should be encouraged to do the same. Such an effort would be consistent with the January 18, 2011, Executive Order regarding Improving Regulation and Regulatory Review [http://www.whitehouse.gov/the-press-office/2011/01/18/improving-regulation-and-regulatory-review-executive-order].

Statistics: It is difficult to understand past, current, and future directions of the domestic aquaculture industry without accurate production and market numbers. The Federal government should track and publish this information through its National Agricultural

Statistics Service. Recent cuts in the census of U.S. aquaculture are inconsistent with the nation's aquaculture policy.

Financing: Due in part to the lack of a clear regulatory climate and the difficulties associated with defining the market, aquaculture startups can have trouble obtaining financing. The Federal government should consider ways to make funding more readily available for properly vetted aquaculture projects.

Information: The U.S. consumer is exposed to many conflicting messages regarding the safety and sustainability of wild, farmed, foreign, and domestic seafood. The result seems to be general confusion and apprehension regarding seafood consumption. The Federal government should provide a source of clear and unbiased information for the consumer. Especially as it pertains to specific consumer concerns (e.g., mercury content, PCBs, and overfishing).

An interagency aquaculture coordinating group, under the Office of Science and Technology Policy, meets on a quarterly basis to better coordinate on aquaculture issues. The group is composed of members of federal agencies with roles in the development and regulation of aquaculture, and is currently proposing a Research and Development Strategic Plan to address these and other issues associated with U.S. aquaculture. Federal support of the Research Plan would be an important initial step toward meeting the proposed challenge.

Meeting this grand challenge - $2 per pound domestically produced seafood - would be a monumental achievement and would dramatically affect the way Americans eat. It would give the U.S. consumer the option to consume seafood in the same way that they now consume chicken breast- or ground beef, and could have important public health benefits. Importantly, it would also be a sign that U.S. aquaculture production is a large and thriving part of the nation's economy, and that the U.S. is a world leader in the industry. It would mean that one of the major seafood markets of the world is no longer dependent on the harvest of imperiled wild seafood stocks or on the low cost production methods of developing countries. As long as high regulatory standards are maintained, it would mean that safe, high quality seafood can be produced in a sustainable manner, without sacrificing the health and function of the environment. This is an attainable challenge. However, the benefits of success would be incremental. If the effort results in the domestic production of $4 per pound, or even $6 per pound seafood, this is still a significant win for the U.S. consumer, the U.S. economy, and the environment.

Bioeconomy White Paper

Georgia Institute of Technology
December 6, 2011

Introduction

Georgia Tech is recognized as one of the top research universities in the world as evidenced by its recent top ten listing by Thomas Reuters.[i] Its six exceptional colleges include the largest engineering college in the United States. Research is conducted in each college and Tech's applied research arm, the Georgia Tech Research Institute. Economic development activities reside in the Georgia Tech Enterprise Innovation Institute including one of the top ten incubators in the country and state-wide outreach effort supported by the State of Georgia and federal programs such as the NIST Manufacturing Extension Partnership (MEP).

Georgia Tech recently defined an industry facing research strategy focused both on leading-edge research and economic development. Most universities pursue a linear, sequential flow of discovery-based research to occasional declaration of intellectual property followed by licensing or company formation/spin-out. In contrast, Georgia Tech pursues a concurrent strategy focused on strategic theme areas spanning biotechnology, energy, nanotechnology, innovative materials, future media, and policy. By concurrence, Tech defines and pursues grand challenge problems and provides thought leadership to the overall research community; seeks to create and sustain collaborative partnerships across the research community; and accelerates the maturation and transition of research outcomes into societal use. A few recent examples include the creation of a national roadmap for robotics announced by President Obama in June 2011, a partnership with GE Energy to focus educational programs in engineering and business on innovative energy solutions (resulting in 21 patent applications in two years), and a streamlined licensing program.

In the area of biotechnology, Georgia Tech leverages its partnership with Emory University and the Morehouse School of Medicine as well as an embedded biotech incubator and a bio-device pilot plant, to concurrently conduct discovery-based and translational research with clinicians, trials, and commercialization. The research-to-commercialization process is as innovative as the research itself. It is in the context of the collective experience of over 7,500 researchers and leadership at the national level that Georgia Tech submits this white paper.

Grand Challenges

Simply stated, we must be bolder. The most useful outcome OSTP can take in response to the Bioeconomy RFI call is to facilitate a return to boldness, an attribute that used to distinguish all aspects of *the American way*. Federally sponsored research programs and accompanying transition efforts sponsored by government and the private sector have become too incremental and risk adverse. What is needed are bold, even audacious, statements of grand challenges to ignite passion and excitement and to push researchers and technologists to do more than they think possible. Too often, current federal programs, notably the National Institutes of Health (NIH), require proof of concept with supporting data prior to proposal submission. This has prompted the joke in the research community that the research needs to be done prior to the application for research support. But "the joke" has produced a *laissez-faire culture* that is symptomatic of life in America today. Our country's willingness to boldly state the equivalent of the "JFK moon shot" or the quest in the 1950s to eradicate the world of polio and TB is sorely missing today.

Grand challenges related to the bioeconomy can take two forms. First, bold statements of research outcomes that transform patient care and health (e.g., a pediatric cardiac value implant that "grows" with the child; patient specific, custom cancer therapies based on genome mapping). Second, bold statements of process improvement that will incentivize and accelerate the transition of research results to use (e.g., process redesign of clinical trials and related policies to yield a 5x reduction in time for approval).

Research and Development

While R&D investments in platform technologies can support advances in health, energy, agriculture and the environment, that alone is insufficient to generate the impact required to meet real world needs. NIH, NSF and other key federal agencies together with certain foundations and non-profits do a good job in supporting the development of basic scientific advances. However, as a country, we do not do enough to help translate those basic science discoveries further down the path toward identifiable product opportunities and hence toward meeting real world needs.

Greater funding emphasis is needed in the area of translational research to move discoveries from the lab bench closer toward a product which serves the patient. Translational activities can be as scholarly as basic fundamental research; the unifying feature is the impact of the discovery on the patient and society. Indeed, the more advanced the discovery, the more creativity is needed in developing innovative animal models applicable to human disease in which to test the safety and efficacy of the new device or drug.

Besides federal support for translational research, dissemination of best practices for translations is also needed. For example, the processes advocated by the Coulter Foundation should be adopted throughout the community.

To be truly impactful, translational activities need to occur on three levels: 1) translational research to apply basic scientific knowledge to real world needs as targeted product opportunities, 2) translational teaching to develop educational methods applied to real world needs for both students and faculty, and 3) translational services – engaging in activities that are responsive to real world needs. This has a direct impact and influence on what skills are needed in the workforce.

Translational research by definition means fast, seamless transfer of discoveries from bench to bedside of high impact problems, i.e., problems which truly address unmet medical needs regardless of the commercial potential of such discoveries. High impact problems are beneficially disruptive technology discoveries. In essence such disruptive technologies are often "platform technologies", underpinned by seminal paper(s), strong international patent positions (i.e., own an area based on strategic considerations of the institution), and have the concept proven in multiple, diverse applicable animal models.

In biomedical research, strong emphasis must be placed on translation of the discovery concept into multiple proof of concept studies in various, robust, reproducible animal model systems which are closely representative of human disease. These animal models must also be acceptable to industry and private investors as a solid proof of concept, actually mirroring the intended use. This may require the development of novel and larger animal models and comparative studies. Comparative studies should directly compare the use of current therapies and devices to the new discovery concept.

Further, we should place emphasis on more early product-oriented development work (e.g., advanced working prototypes actually tested in representative animal systems, therapeutics that are formulated and basically characterized as to pharmacokinetic, pharmacodynamics and pharmacological properties, and consideration of other common product developmental hurdles such as sterilization, clinical trial supplies,

safety and tolerability, as applicable). This level of translational research will help assure the project is attractive to a potential industrial partner or to a venture investor.

Translational teaching aims to educate well-rounded future innovators. Students too often may not pursue careers as pure academics and are increasingly seeking practical training for their careers. To meet these needs, academic program faculty, together with other experts in the institution, should provide integrated training in areas such as market research (lecture and lab), MBA essential skills (management, communication, and finance), intellectual property and legal essentials, drug and device product development and regulatory approval processes, and commercialization. The newly proposed Biomedical Engineering Master of Science Degree Program Proposal for Biomedical Innovation and Development (BiolD) at Georgia Tech is aimed at addressing some of these needs. Programs such as Georgia Tech's Technological Innovation: Generating Economic Results (TI:GER), which serve to integrate technology and business approaches under the guidance of an industry-experienced mentor, could be expanded.

As important as our students are, it is equally important to have programs for mentoring faculty in product development processes, regulatory, commercialization and to recognize translational research as a scholarly activity.

Translational service refers to the engagement of faculty and students in activities responsive to real world needs, specifically, to apply their innovative discoveries to address unmet medical needs and societal needs.

Moving life science breakthroughs from lab to market

Product development skills are often limited in academic institutions and need to be acquired and rewarded. Academic institutions can learn from industry: different skills are required to create a new scientific discovery and to then translate and develop that discovery into a product. Hence, the nature and type of people and skill sets required to effectively carry out translational research activities are often different. This is particularly salient in the context of how academic institutions evaluate faculty members.

Translational research is a discipline within its own right and it is the scientific quality by which it should be judged. Similarly the translational scientist, to do it right, must be able to bridge/design the preclinical work with a forward look toward the clinical, regulatory, and commercial paradigms. All of this translates into opportunities for publication in peer reviewed journals, grant funding, and industry funding. Translation, to be successful, requires other factors such as IP protection, understanding of product development, industrial involvement, and licensing. These could serve as other factors meaningfully considered and appropriately weighted in faculty promotional assessment.

Funding for translational research/ early-stage product development is limited and should be enhanced. The federal government could undertake more extensive funding as part of a grander Translational Research Initiative. The funding could be differentially applied. For products with reasonable commercial potential, federal funding could extend through the following phases: development and robust animal testing of operational prototypes. The prototypes would then be licensed to industry to finish product development and gain regulatory approval for marketing. For products with little commercial potential but high unmet medical need, the governmental funding would be extended through to the development of fully operational devices, not just prototypes, for use under humanitarian device or drug exemptions in a single institution. Such products could then be made available to other institutions on a needs basis. The "finished" product might eventually be attractive to industry as significant product development risk would have been eliminated. In either of these applications, it is important to involve experts with industry R&D, product development, and business experience to guide development of new devices and drugs.

Recommendations: Imbed distinct translational research and product development experts within academic departments, as applicable. Coordinate, through collaborations, basic academic research and translational group endeavors recognizing the differences between discovery and development in order to most expeditiously advance projects from discovery through early product development.

a. Develop a strategic approach to which areas of scientific research and discovery an institution is an expert in and align translational activities with the institution's discovery strategy.
b. Consider adding a new group of academic researchers who are experts in the various downstream activities associated with translating discoveries into products – i.e., small through large animal research with an emphasis on model development and characterization of its fit to human diseases and subsequent characterization of new product concepts in these models; medical device design, prototype, scale up and associated activities; pharmaceutical development and pK and pD characterization for potential therapeutics. Ideally, these researchers should have strong industry experience in product development.
c. Establish formal educational programs for faculty, staff, and students in product development of medical devices and therapeutics. This would include a basic understanding of the development processes and supporting activities including manufacturing, regulatory, quality, and safety both domestically and internationally. Such activities are unique to the medical industries.
d. Utilize existing relationships with clinical colleagues at clinical research institutions and in the medical community to add continued strong clinical input to project development and assessment.

Academic institutions tend to loosely coordinate discovery and development activities. The process of translating discovery breakthroughs into product realities is extremely complex. Industry has effectively dealt with these complexities by establishing project teams which bring to bear the required functional expertise in a unified project team; academic institutions could apply and benefit from these principles.

Recommendations:

a. Coordinate translational research and discovery endeavors. Establish a function focused on establishing the coordination of activities from discovery through early development and which brings product development and commercial understanding in advancing strategically important projects. The skills to drive this require industry trained experts who understand the discovery, development, and commercialization processes for both devices and therapeutics and can bring these understandings to bear in an academic environment. The ideal individuals should also have the scientific credentials to engender respect within the academic environment. This coordinated effort should function as a project team to assure a smooth transition of discoveries into products and help speed project throughput.
b. Establish shared objectives for translational research programs. Align all functions supporting technology development and its subsequent commercialization with a common set of shared objectives and goals. By supporting functions this could include licensing/tech transfer, patenting, industrial sponsor/support programs, or bioscience commercialization support functions. An institution can therefore present a common, unified front to commercial partners.
c. Manage conflict of interest considerations**.** Recognize that an institution's strategic emphasis on commercialization and faculty (and supporting staff) involvement in commercialization may present challenges to emerging standards of conflict of interest. Consider establishing a working group aimed at melding emerging expectations regarding conflict of interest with the strategic goals of an institution toward commercialization and does so in a fluid and flexible manner. This may require a cultural shift toward accepting greater, though still maintaining prudent, risk-taking.

d. Foster greater industry involvement. Consider establishing a formal program/process to encourage the establishment of embedded biomedical industry laboratories on campus and which are responsive to both industry needs and academic needs. This would include, amongst other items, office and lab space, protection and sharing of IP, collaborative involvement of industry scientists with corresponding faculty and/or students on campus, streamlined business and technology licensing practices.
e. Establish mechanisms to access 3rd party translational funding from government, industry, foundations, alumni, interested community business people and private investors.
f. Leverage existing programs supported by the federal government and the states. For example, the NSF Innovation Corps model is an excellent initiative designed to accelerate the commercialization of NSF-funded research. Furthermore, efforts such as the Manufacturing Extensions Partnership could be leveraged to support more rapid technology transfer and adoption.

Workforce Development

As previously noted, students are increasingly seeking practical training for their careers and, as such, students provide the marketing "pull" to adapt educational programs. It is equally important to have programs for mentoring of interested faculty in bioscience product development processes, regulatory, commercialization and the evolving health care environment.

Recommendations:

a. **Establish formal faculty/student educational programs in the following areas:**
    1. **Product development run by industry experts and tailored to faculty/project stages and interests**. This should include industry consideration of what constitutes sufficient proof of concept, regulatory, quality, manufacturing and clinical activities. The expertise to organize and manage such a program exists within an institution; resources could be reallocated and/or supplemented with external experts
    2. **Patenting and management of the process from discovery through patent issuance**. The considerations for bioscience projects tend to be rather distinct from other areas.
    3. **Business development related to commercialization of inventions including aspects of project commercial evaluation, competitive assessment, and company formation/management, funding, and partnering strategies.** Much of this might be done in conjunction with the College of Management and existing ATDC commercialization catalysts and expansion of TI:GER to include faculty.
b. Establish a commercial mentorship program for each faculty project.

Reducing regulatory barriers to the bioeconomy

Patent Budgets: A significant constraint for many public and private institutions is reflected in their limited budgets to globally protect intellectual property funded by federal research dollars. This constraint forces institutions to make a choice: not file for patent protection or limit the regions of the world in which they file. Given the early stage nature of most discoveries, so initial research is conducted without the benefit of knowing the commercial scope or potential of these discoveries. Most biomedical discoveries will require an industrial partner who can provide the enormous investments in product development required to gain approval to be marketed. As most drug and device companies now operate globally, when academic institutions do not file for patent protection or do so only in the US, the likelihood of a commercial partner being interested in licensing that discovery is significantly diminished. An industrial

partner will not invest, even when there is large commercial potential, if there is no patent protection to protect their investment in product development and help assure that they can recover their investment. Further, if there are two competing technologies, industry is likely to choose the technology which has global IP protection over a technology, even if better, which only has IP protection in a more limited geography.

The technology development model needs to shift from cost-recovery toward investment. Most research institutions tend to view their investments in technology transfer, licensing, and intellectual property protection from a cost recovery rather than an investment perspective. A new federal funding vehicle could be established to provide resources to U.S. academic institutions to help jump start efforts to globally patent appropriate discoveries and to focus on the translation of discoveries into products. To truly jump start translational research efforts in institutions, specifically those without existing medical schools, requires investment in research facilities to include labs, offices, vivariums, equipment; acquisition of new product development-oriented faculty; and establishment of translational research training programs. Funds to jump start such endeavors could be handled as center or block grants to integrate translational research and technology development into the mainstream of our research institutions which do not currently have medical schools. Since translational activity to realize medical device and/or drug prototypes takes time, the grants should have a funding life of at least five to eight years. To encourage investment in IP protection and in more effective technology development and licensing, those institutions which realize success from enhanced licensing endeavors could receive incentive matching funding from the Federal government to further expand their efforts. Success could be defined as: 1) licensing the technology to a commercial partner for further development, 2) realizing an FDA approved device under a humanitarian exemption for patient use within affiliated institutions, or 3) establishing an embedded industrial laboratory within an academic institution where the laboratory creates a collaborative working relationship between the academic discovery oriented investigators and the product development oriented industrial scientists.

Unreasonable Conflict of Interest Management. More reasonable and pragmatic standards in conflict of interest (CoI) management need to be established. These standards would provide ‘safe harbors’ for academic investigators and affiliated support personnel working with industry that encourage, rather than discourage, interactions and collaborations. In addition, they would, foster establishment of product licenses and start-up enterprises and allow the effective use of unique academic facilities and equipment to benefit the new enterprises. Such standards should reflect the low probability of realizing a product and should be based on realities. Appropriate quality assurance oversight could be established to audit and assure data integrity in those instances where there are concerns. Federal agencies struggle with these very issues. The heads of DHHS/FDA have indicated intent to modify their CoI policies as current policies have limited their ability to fill vacancies on key advisory panels.

Public-private partnerships

Embedded industry-academic laboratories have proven to be successful when appropriately managed.

Tax-incentives could be provided to industry for sponsored research, embedded laboratories and collaborations with academic institutions. Existing tax incentives, generally limited to unrestricted donations, could be expanded to include collaborative targeted research and product development initiatives.

Partnerships with industry in generalized funding of product and technology development can benefit from a combination of tax incentives and sharing of future economic returns. The funding could come from private industry, and private investors, other accredited investors and even the public at large. This

funding could function loosely as an internal venture fund focused within an academic institution on furthering the economic development of its technology. The Georgia Research Alliance, in part, serves as an example, but its reliance on State funding requires supplementation to be more effective.

Conclusion

In order for the U.S. to truly harness biological research innovations in an effort to meet grand challenges, we must make bold, game-changing steps. By focusing on translational research and processes, mitigating barriers, and providing robust programs for faculty and students, we can move beyond incremental changes and, instead, create transformational impact in the fields of patient care, health, and the transition of research results to use.

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[i] http://www.timeshighereducation.co.uk/world-university-rankings/2010-2011/engineering-and-IT.html

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December 6, 2011

University of Illinois Response to the OSTP Request for Information on Building a 21st Century Bioeconomy

University of Illinois faculty, staff, and students conduct millions of dollars in biological research every year. This research leads to innovations and technological advances. When this technology is commercialized, it can lead to new jobs and even to new industries. These industries need skilled workers, and universities train those workers to succeed, innovate, and start the cycle over again. Because we are so clearly a part of the Bioeconomy, the University of Illinois appreciates the opportunity to provide comments to OSTP regarding the Administration's Bioeconomy Blueprint.

Indeed, scientists on our Urbana campus are pursuing some of the country's most important biological research in genomics and medicine, looking for critical solutions to drive energy independence, developing cutting-edge materials to enable advanced manufacturing, and pursuing novel solutions to information technology challenges. Our Chicago campus, with its medical school and healthcare system, receives millions of dollars in federal funding to address health disparities by developing novel drugs, innovative treatments, and social programs. Additionally, research at our Springfield campus contributes to the policy and education aspects of the Bioeconomy.

A 21st Century Bioeconomy has many components, but at its heart is a robust, thriving research enterprise that enables the innovation and creative thinking that advances job creation and commercialization activities. Simply put, any "blueprint" for building a Bioeconomy for the 21st century must incorporate an aggressive and robust research portfolio.

In response to Question #5, "What are the barriers preventing biological research discoveries from moving from the lab to the commercial markets?," we believe that the federal government should take an active role in supporting commercialization efforts that move discovery from the lab to the marketplace. The University of Illinois has embraced its role in economic development and has put in place a series of resources and initiatives that demonstrate this commitment. The Research Park, which was just named the 2011 "Outstanding Research Park" by the Association of University Research Parks, is perhaps the most visible. Home to more than 90 companies employing more than 1,200 people, the

Research Park provides internship opportunities for students, resources for faculty to commercialize new technology in conjunction with academic work, and engagement opportunities for companies who want to collaborate with the University of Illinois.

Additional programs that support entrepreneurship and economic development at the University of Illinois include:

Licensing and Commercialization: The University of Illinois is the sixth leading source of patents in the state of Illinois and the only university in the top ten. In fact, our efforts to encourage our faculty to think entrepreneurially yielded a record number of start-up companies in fiscal year 2011. Additionally, the Offices of Technology Management on the Urbana and Chicago campuses have significantly increased revenue from licenses and options over the last several years, to more than $19.08 million in fiscal year 2011, up from $9.03 million just five years ago. In 2010 and 2011, both campuses created proof-of-concept funding programs to help advance development and attract licensing partners for our high-potential technologies.

Startup Support: EnterpriseWorks is a small business incubator that helps fledgling companies succeed by providing an array of shared facilities, equipment, and support services (such as the Entrepreneur-in-Residence program and the I-Start professional launch) as well as weekly programming, educational forums, and social networking opportunities to encourage collaboration. Since opening in 2003, EnterpriseWorks incubation facilities have become the launching pad for 127 startup companies, over half of which spun out of a University research lab.

Venture Capital: In 2000, the U of I conceived of a venture capital fund that would invest in companies derived from faculty-based research, and in 2003, IllinoisVentures invested in its first portfolio company. To date, IllinoisVentures has had extensive impact on the vitality of the Illinois economy, investing $38 million in 69 startups that employ technology from the U of I and other Midwest universities and federal laboratories. These companies have created more than 450 jobs and have raised over $450 million from other funding sources – an impressive 12:1 leverage ratio.

Additional Activities: The Chicago campus, together with the National Institutes for Health (NIH), became the first in the world to share patents with Unitaid's Medicines Patent Pool, which makes new medicines more affordable in developing countries. The Urbana campus developed a unique label license that will encourage broad industry adoption of a portfolio of technologies that has the potential to greatly enhance the syntheses of many chemically important small molecules, such as pharmaceuticals and natural products.

The University's initiatives as described above each contribute to the evolution of a new university culture – one that invests in and rewards entrepreneurial pursuits, and ultimately fosters economic development and advances the country's global competitiveness. Since 2000, the University has increased its research budget by more than 50% to over $900 million today, catapulting it to the top Illinois research university. Likewise, the pace of startup company formation, patents and licensing activity, and

collaboration with industry continues to increase over time, providing significant and demonstrable economic impact and serving as a national benchmark. As the University of Illinois looks toward the 150th anniversary of the Morrill Act, we assert that it is time for the reinsertion of the American Research University as the renewable source of innovation and driver of our Bioeconomy.

We would be pleased to answer any additional follow-up questions. Feel free to contact me should you wish to discuss these issues further.

Sincerely,

Lawrence B. Schook
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Novozymes North America, Inc.

NOVOZYMES RESPONSE: REQUEST FOR INFORMATION: BUILDING A 21ST CENTURY BIOECONOMY

Creating the Building Blocks for a Bio-Based Society

Novozymes applauds President Obama for his initiative to develop a bioeconomy blueprint and improve America's health, food, energy and environment through science and innovation. We believe the future of America is contained in these pages.

Like the President, we imagine a world where everyday products are made with organic materials instead of oil:

- Transportation fuels made from agricultural and forestry waste and non-food energy crops, that burn up to 90 percent cleaner than gasoline
- Detergents that clean thoroughly in cold water, reducing energy consumption, consumer spending and water pollution
- Plastics and polymers based on renewable biomass – not petroleum
- Renewable chemicals that are less harsh to the environment
- Food crops that require less fertilizer and water, yet produce higher per-acre yields
- Animal feed that promotes greater nutrient absorption, and reduce harmful by-products in animal waste

These are the building blocks for America's bio-based society: a sustainable, low-carbon approach to energy and production processes in which renewable materials can meet the growing food and product needs of an expanding population at a time of scarce resources.

Biology as an Economic Engine

The United States is poised to be the leader in the development of the bioeconomy, combining biotechnology innovation, agriculture productivity and manufacturing expertise. Biotechnology will create 21st century innovations, jobs and sustainable economic growth. We believe many of those innovations and jobs will be rooted in renewable energy.

Americans are looking for less expensive, domestically-produced and cleaner ways to fuel their cars and trucks. In a new University of Texas poll focused on energy issues, Americans said their top concerns were U.S. consumption of foreign oil and the country's progress in developing renewable energy. Biofuels are meeting those needs.

Today the American biofuels industry provides more transportation fuel to the U.S. market than we import from Saudi Arabia. In 2010:

- ethanol production contributed $53.6 billion to the nation's Gross Domestic Product and generated $8.6 billion in federal tax revenues; and
- taxpayers were saved $39 billion that would have otherwise been sent to foreign countries by replacing 445 million barrels of oil with biofuels.

Converting biomass into fuels, energy and chemicals has the potential to generate upwards of $230 billion to the global economy by 2020, according to the World Economic Forum. Two challenges remain in realizing the potential of a bioeconomy in the United States:

1) Commercialization of the industrial biotechnology sector, including advanced biofuels and other biobased products; and
2) Increased public awareness on the potential and the benefits of bioenergy and the bioeconomy.

Providing a stalwart signal of support to the private investment and consumer market is where the federal government can have significant impact.

Recommendations

Legislative

- Insist on protection of the Renewable Fuel Standard as enacted in the Energy Independence and Security Act of 2007
- Call for reauthorization and mandatory funding of the Farm Bill Energy Title programs, in particular the Biomass Crop Assistance Program (BCAP) at USDA
- Support authorization and strong funding for Department of Energy biomass programs
- Continue to support the strengthening of the Department of Defense and US Military by calling for a strategic biorefinery initiative between the Navy, DOE and USDA
- Establish a federal matching grant program to fund projects to repurpose or retrofit existing idle or underutilized manufacturing facilities for the production of advanced biofuels and/or renewable chemical
- Establish a Synthetic Biology Research and Development (R&D) Grants Program
- Establish an Industrial Bioprocess Research & Development (R&D) program
- Strengthen and expand the USDA's BioPreferred ™ Program
- Because, the most fungible currency for a bioeconomy is sugar, reduce the cost of producing sugars from a diverse array of starch and biomass sources and to develop pathways from these sugars into fuels and renewable chemicals
- Support deployment of pioneering biorefineries that are demonstrating the commercial viability of using biomass based sugars

Regulatory

- Ensure that solicitations are coordinated across agencies such that all links in the value chain for new technologies receive funding in proportion to the technical challenges associated with each link
- Encourage multi-disciplinary, multi-institutional research programs
- Government labs should continue to play an important validation/verification role
- Government labs should position themselves as a link between basic research and commercial deployment
- The government should create a stable regulatory and financial environment for the deployment of advanced biofuels, and should mitigate infrastructure obstacles
- Obvious differences between biogenic and fossil fuel sources of GHG emissions should be recognized in regulatory programs
- Indirect emission impacts, such as indirect land use change should not be included in life-cycle analysis absent internationally recognized methodologies
- Regulations should ensure a level playing field between bioproducts and their incumbents
- Market and regulatory barriers to adoption of biofuels and other biobased products should be removed

About Novozymes

Novozymes is a technology and science company focused on bioinnovation; we respect and encourage both. We have more than 5,000 patents and 700 products at work in 130 countries: enzymes that remove trans-fats in food, lower the temperature needed to wash a consumer's clothes, and convert renewable biomass, from switch grass or corn stover, into biofuels. Our technology saves consumers money, creates domestic jobs, increases national security, and protects the environment for our children by making wise use of our natural resources.

Today, we are nearing completion of a new state-of-the-art bioinnovation plant in the Midwest, a $250 million investment in America's future. Our Blair, Nebraska enzyme facility has already created 140 construction jobs and will bring 100 permanent jobs when it opens in 2012. In fact, 45 full-time employees are already at work. These are good-paying, sustainable jobs for families creating sustainable energy for our country. President Obama has been invited to the groundbreaking of this facility in May 2012.

As this investment demonstrates, we believe private industry plays a critical role in the success of America's economy. However, we also believe a strong partnership is vital to the success of any emerging industry, where the private sector provides the innovation and lion's share of capital to develop it – and the public sector provides consistent policy support to grow it.

At Novozymes, we believe fundamental, long-term change in the energy, industrial, and agriculture sectors is required for sustainable global growth. The world needs more than just short-term solutions that simply reduce the negative effects of current technologies, actions, and policies. With our breakthrough enzymes that drive greener, more efficient industrial processes, Novozymes is advancing the technologies and industries that will drive future economic growth and job creation.

On behalf of Novozymes and its 829 employees across America – from California, Wisconsin and Nebraska to North Carolina, Virginia and Maryland – we thank you for the opportunity to submit responses to the following "grand challenges" identified by President Obama:

(1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

The grand challenge for the advanced biofuels industry at this point is commercialization, moving from our proven science and technology and demonstrated impact on consumers to large-scale production within the United States. The advanced biofuel industry has done an extraordinary job, in a short period of time, overcoming technical and scientific challenges. Now we need to see steady public support for the industry in order to compete with Big Oil and attract the innovative first movers in the private investment space.

The federal government can help US companies and technologies win the race for the next energy gold rush and keep jobs and technology in this country by implementing the following policy priorities:

Maintain the Renewable Fuel Standard enacted in the Energy Independence and Security Act of 2007. This important policy is seen not only as a market driver for renewable fuels but also as a signal to the private investment community that the public sector values and supports this industry. In order to grow beyond the current industry and commercialize cellulosic and other advanced biofuels in an expedited way, the integrity of the RFS, and government support, cannot waiver.

Reauthorize and fund the Biomass Crop Assistance Program (BCAP) at USDA. BCAP is the key program encouraging and facilitating farmers and landowners to produce new purpose grown energy crops (PGECs) for advanced biofuels and biobased products. Developing the feedstock portion of the value chain is extremely important for bioproducts such as the increasing cellulosic biofuel volumes required in future years for the RFS.

Continue to authorize and fund government biomass programs. Such as the Biomass and Biorefinery Systems R&D Program, ARPA-E, Office of Science, Biological and Environmental Research and Basic Energy Science Office at the Department of Energy to continue the development of new technologies.

Strengthen the Department of Defense and US Military by continuing to pursue a strategic biorefinery initiative. This effort would aid in developing and commercializing alternative, domestically produced fuels qualified for military and aviation use which means our military would be less vulnerable to changes in both energy supply and price. DOD should pursue a strategic biorefinery initiative by establishing a DoD Strategic Biorefinery Deployment Program to finance construction of the first 5 commercial military advanced biofuel biorefineries to meet their alternative fuel goals and be given the authority for long term off take agreements.

Increase public awareness on the potential and the benefits of bioenergy and the bioeconomy. In the United States, there is ample market availability for many forms of alternative energy and other renewable products, the technology readiness and future of the biotechnology industry does not receive adequate attention, particularly when compared to other alternative technologies such as electric vehicles, solar and wind. Most biofuels focus is around the existing biofuels industry. There is more awareness of advanced biofuels than we have seen in the past, but still a limited knowledge base. This should be expanded to increase public support.

Establish a federal matching grant program to fund projects to repurpose or retrofit existing idle or underutilized manufacturing facilities for the production of advanced biofuels and/or renewable chemicals.

Establish a Synthetic Biology Research and Development (R&D) Grants Program. This type of program would fund research and development in industrial biotechnology for the enhanced sustainability of biofuels and renewable chemicals produced through synthetic biology technology.

Establish an Industrial Bioprocess Research & Development (R&D) program. An R&D program such as this would fund projects in industrial biotechnology for renewable chemicals, biobased products, and renewable specialty chemicals.

Strengthen and expand the USDA‘s BioPreferred ™ Program. Building a policy purchase mandate based on federal agencies and contractors purchasing renewable chemicals and biobased products would be very impactful. Expanding the list of products

and uses, particularly for upstream renewable chemicals production rather than just downstream products, would result in a significant increase of use.

Research and development: R&D investments, particularly in platform technologies, can support advances in health, energy, the environment, and agriculture, and accelerate the pace of discovery in fundamental life sciences research.

(2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

With constrained budgets, the Federal government should concentrate the majority of its funding on a select group of thrust areas of critical importance to the nation, one of which should be transitioning to the production of biobased products as a means to reduce dependence on petroleum imports. The government should take a more active role in steering funding programs which enable platform technologies that will impact the bioeconomy in a way that ensures that systematic progress is made, through the following means:

Ensure that solicitations are coordinated across agencies such that all links in the value chain for new technologies receive funding in proportion to the technical challenges associated with each link. In the case of advanced biofuels, for example, this would mean execution by the government of systematic, collaborative programs that are designed to optimize all unit processes in the production of these biofuels. For the conversion of biomass to sugars through a biochemical pathway, this would include an integrated optimization effort around biomass pretreatment, enzymatic hydrolysis and synthesis of fuels from biomass sugars, ensuring that an overall optimal solution is achieved.

Encourage multi-disciplinary, multi-institutional research programs. The Federal government -- and in particular the Department of Energy -- has done a good job of encouraging multi-disciplinary, multi-entity projects including representation from academia, government laboratories and private industry. These diverse perspectives and skills are critical in addressing the complex problems associated with new technologies.

The most fungible currency for a bioeconomy is sugar. Therefore, a major thrust for Federal funding efforts should be to reduce the cost of producing sugars from a diverse array of starch and biomass sources and to develop pathways from these sugars into fuels and renewable chemicals. The Department of Energy has provided substantial funding for research on converting biomass sugars into fuels and chemicals.

The primary product of any biorefinery concept supported by the Department of Energy must be a biofuel. Given DOE's mission, this constraint is understandable, but may distort the rollout of the biorefinery industry. Market forces could dictate a more varied or product neutral bioeconomy in which the first biorefineries are producing higher value products, such as renewable chemicals. This is perhaps where the Department of Agricultural could play a larger role. While DOE has funded large, industry-led consortia to develop biofuels, the USDA has not provided comparable funding for renewable chemicals and other bioproducts, although it seems a natural role for the USDA. **We therefore recommend that the USDA take a leadership role in providing funding for large, industry-led consortia to develop renewable chemicals and other bioproducts.** The USDA must also lead the development of feedstocks for the bioeconomy.

(3) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

Discovery of biocatalysts and creation of synthetic organisms are critical technical areas which underlie our ability to develop a sustainable bioeconomy. Tools which are utilized in these technologies are ones which may accelerate progress across multiple industries.

One current technical challenge is in high-throughput protein expression and characterization. Investment in technologies that allow researchers to express and assay proteins in a truly high-throughput fashion is a way to ensure that the vast genomic sequence data currently being generated can be explored rapidly. In particular technologies are needed to allow for proper require post-translational modifications, such as folding, proteolytic processing, and glycosylation. An example of a high-throughput functional characterization technology would include the substrate-on-a-chip approach with easy product read-out. Substantial improvements in the area of in vitro transcription/translation systems, coupled an automated fashion with micro-high throughput assay systems could make an impact in this area.

Another area of investment should be in decreasing costs of DNA synthesis, particularly for synthesis of large molecules >10 kb. Current prices are around 70-80 cents per base for synthetic DNA fragments in the 1-2 kb size range. In order for ultra high throughput synthetic biology to become a reality, the cost needs to be much lower, on the order of a penny per base or lower. The capability to assemble 50-100 kb size molecules needs to be improved. Some companies are already pushing the envelope in synthetic biology approaches to enhance expression of pharmaceutical proteins (by combinatorial shuffling promoter/enhancer elements, signal peptides, various domains, etc). One can certainly imagine that extremely cheap DNA synthesis will greatly accelerate these applications,

and in addition will enable microbial genome design for biosynthesis of biofuels, chemicals, and even enzymes.

(4) The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

Moving life sciences breakthroughs from lab to market: It is a challenge to commercialize advances in the life sciences because of the risk, expense, and need for many years of sustained investment. The Administration is interested in steps that it can take directly, but is also interested in encouraging experimentation with new private-sector-led models for funding commercialization of life sciences research.

As described in our response to the previous question, this issue clearly relates to technologies for high-throughput expression and characterization. Advances in this arena would potentially add greatly to the ability to predict function. Having a much larger database of characterized proteins would give much greater power to the purely bioinformatic approaches of predicting function such as clustering, tree building, motif scanning, and structure prediction. High-throughput structure determination would additionally add to the predictive power, and this is already occurring to some extent. Better tools for gene model prediction would also be helpful since many of the gene models currently being generated are incorrect and can lead to incorrect functional predictions.

(5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

Support deployment of pioneering biorefineries that are demonstrating the commercial viability of using biomass based sugars. Novozymes believes that it is critical for DOE to follow through on supporting the deployment of near-term proven technologies (*eg.*. cellulosic biofuels) and not be overly distracted by promising but highly uncertain (from both a technical and economic standpoint) technologies that are many years from commercial realization. We encourage Federal agencies to allocate the necessary funds to ensure that novel technologies can cross the "Valley of Death" and be commercialized within the U.S. Otherwise, the benefits accruing from technologies developed in the U.S. could be harvested elsewhere.

Government labs should continue to play an important validation/verification role -- Government labs are in a unique position to objectively compare novel energy technologies. Industry and often academia have a vested interest in particular technologies and cannot provide independent assessments of nascent technologies.

Government labs should position themselves as a link between basic research and commercial deployment -- Government labs should not try to duplicate basic research performed by academic labs, but should instead conduct research to help bridge the gap between basic research and commercial deployment. Government labs should be encouraged to work closely with industry to transition technology into the marketplace.

The government should create a stable regulatory and financial environment for the deployment of advanced biofuels, and should mitigate infrastructure obstacles – the government should, through legislation and regulation, provide a stable environment so that proven energy technologies can be deployed/commercialized and allowed to mature with concomitant reductions in cost.

(6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?

Although it does not benefit our company directly, we believe the SBIR/STTR program provides a greatly needed source of funding for startup companies and has led to the development of many groundbreaking technologies. It is one of the only sources of funding that these companies have available to them that does not include giving over a substantial portion of the equity in the company.

(7) What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

In line with our recommendation that government labs serve a validation/verification role, we believe that independent, objective analysis and testing by government labs of new technologies is very useful to companies considering the further development of or investment in these technologies. As an example, NREL's report entitled "Process Design and Economics for Biochemical Conversion of Lignocellulosic Biomass to Ethanol" serves as the only publicly available benchmark for the conceptual design of an advanced biofuels production plant. It serves as a baseline for our own process models for advanced biofuels.

(8) What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

The challenges associated with existing private-sector models for financing bioeconomy firms is centered on building an extremely high level of trust with the institutional investors to help catapult their business model toward commercialization. Investors are seeking rates of returns that remain out of reach for many of the first-to-market players. For the advanced biofuel producer, the cost of capital remains high and attracting investors in this economy is proving to continue to be a challenge. As the dialogue continues, investors and producers are finding creative ways for securing financing given these challenges. The path for success comes down to trust in the industry, the business, the team guiding them forward and security in the market and public support.

Strategically, companies that invest heavily in an experienced and exceptionally strong executive management team, board of directors and advisors are moving quickly in securing needed capital from investors. These companies are finding it much easier to gain the assurance required to secure the funding needed to overcome the so-called "valley of death". On a tactical level, these solid teams know what investors need to develop that level of certainty. Some tactical examples surfacing that help secure the capital they required are centered on securing long terms feedstock agreements for their plants, proving their technology with economically viable results, providing strong business and economic models as well as executing on solid off-take agreements.

Federal agencies can address these challenges by taking on slightly increased risk, as they have historically done, and focusing specifically on the pieces of the value chain highlighted above – feedstock development and production, continued research and development for processing technologies and the ability for federal agencies to act as a secure customer of these technologies by providing long term purchasing agreements. All with the goal of reducing costs and increasing private sector confidence.

Workforce development: Investment in education and training is essential to creating a technically-skilled 21st century American bioeconomy workforce.
(9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Academia, the government, and private industry should work together to make internships and apprenticeships in private industry more readily available. North Carolina has a good example of a program that helps ready Ph.D.'s for industrial research careers. The North Carolina Biotechnology Center's Industrial Fellowship Program "provides the state's

Ph.D. scientists with an opportunity to gain industry experience and companies to benefit from new talent and expertise. The program is for recent doctoral graduates and postdoctoral fellows who would like to transition from academia to permanent employment in the state's life sciences industry."

(13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

Toxic Substances Control Act (TSCA) Inventory Nomenclature - USEPA

(a) On Nov. 15, 2004, the EPA announced that it is considering new procedures and regulations for naming enzymes and proteins when listing these substances under the Toxic Substances Control Act (TSCA) Inventory. The EPA is considering modifications to the procedures and regulations that govern the naming of enzymes and proteins as they are listed in the TSCA Inventory. Currently, the naming procedure focuses on the function of the enzyme. However, EPA is now proposing to expand the requirements of the naming procedure to include the source, process, and amino acid sequence of the enzyme or protein.

Enzymes and host organisms have been modified to enhance performance in industrial and food products since they were first commercialized. Moreover, modified enzymes that are used in EPA-regulated products, such as detergents, textiles, fuel ethanol, pulp, and paper have produced no known new risks beyond those already identified for enzymes in general.

(b) The justification for the proposed procedural changes remains unclear and possibly statutorily insufficient. EPA's authority to regulate chemical categories is evident in section 26(c) of TSCA, which specifically provides that any action the agency is required to take concerning a single chemical substance may be taken also with respect to a category of chemical substances. This proposed rule appears hold enzymes to a standard not applied to other materials listed on the TSCA Inventory for unclear reason(s), which could discourage innovation and commerce.

(14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

The obvious differences between biogenic and fossil fuel sources of GHG emissions should be recognized. The U.S. Congress has worked diligently to develop definitions of renewable biomass for authorized bioenergy and bioproducts programs such as the Renewable Fuel Standard that preclude the use of biogenic carbon from unsustainable sources. Therefore, biogenic carbon accounting framework should not be overly

complicated or burdensome. In addition, methodologies applied to biofuels and other bioenergy sources should apply uniformly to all end uses.

Indirect emission impacts, such as indirect land use change should not be included in life-cycle analysis absent internationally recognized methodologies that enjoy widespread consensus in the scientific and economic communities. The government should promulgate regulations that depend on estimates of indirect land use effects only when these effects have been calculated using robust, scientifically defensible models that have been rigorously reviewed by expert scientific panels. Further analysis of complex and controversial ILUC models is needed.

Regulations should ensure a level playing field between bioproducts and their incumbants. A level playing field enables introduction of new products and process pathways in order to maximize opportunity for innovation and to remove barriers for market entry.

Environmental benefits of industrial biotechnology should be sufficiently and consistently rewarded in the regulation of precedent-setting climate programs (e.g. cap and trade, LCFS).

Market and regulatory barriers to adoption of biofuels should be removed. This could be transportation fuel infrastructure upgrades such as increased production of flex fuel vehicles, blender pumps, additional refinery and pipeline capacity.

(15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

US Food and Drug Administration (FDA)
Docket No. FDA–1997–N–0020; Formerly Docket No. 1997N–0103; Substances Generally Recognized as Safe (‘GRAS’)

Over the last thirteen years, the FDA’s Center for Food Safety and Applied Nutrition (CFSAN) has gained significant experience under the framework of the 1997 proposed rule (62 FR 18938) and reviewing hundreds of GRAS notifications for human food. In June 2010 the FDA’s Center for Veterinary Medicine (CVM) announced a pilot program and start to review GRAS notifications for animal feed; unfortunately, only three submissions were reviewed 9 months after this announcement (see link at: http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/GenerallyRecognizedasSafe GRASNotifications/ucm243845.htm).

The vast experience highlighted by CFSAN in its "experience document" provides valuable learning that can be of benefit to CVM and therefore the food and feed industries. Both CFSAN and CVM should strive for harmonization of their requirements and policies, so the process is not more stringent for one industry than the other.

The Pesticide Registration Improvement Renewal Act (PRIA) - USEPA

(a) The Pesticide Registration Improvement Renewal Act (PRIA) requires EPA to conduct the review process within a defined time period. Unfortunately, the EPA has difficulty meeting the mandated timelines. Some of the mandated decision times being proposed for PRIA 3 (effective Sept. 2012) are being extended by at least 50%, with an additional time requirement for final label approval. For example, B580.86 approval may increase from the current 18 months to as long as 27 months.

(b) The Federal Insecticide, Fungicide, and Rodenticide Act (or FIFRA), Section 33 (e) directs EPA to identify and evaluate reforms to the registration process with the goal of reducing review times for applications. Novozymes would like to see the agency focus more on identifying these reforms and refrain to unilateral extension of mandated decision timelines in PRIA 3. (Note: In 5+ pages of proposed changes to the Biopesticide section, none of the times are decreased. Nearly all reviews are increased by 2-12 months, plus the additional 1-3 months for final label review). Additionally, EPA has established a "fast track" regulatory review process for "safer pesticide alternatives" for new technologies that meet the criteria. Novozymes would like to see EPA's BPPD identify opportunities where reduced-risk products could be accelerated through the registration process, without sacrificing the scientific integrity of evaluation process. One can further accelerate the registration of a new active ingredient by being encouraged to submit for a joint USEPA/Canadian review, with the incentive being a (US) Federal review time as low as 12 months.

Pesticides; Policies Concerning Products Containing Nanoscale Materials - USEPA

(a) EPA seeks comment on several possible approaches for obtaining information about what nanoscale materials are present in registered pesticide products. One possible approach would involve using section 6(a)(2) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to obtain information regarding what nanoscale material is present in a registered pesticide product and potential effects on humans or the environment. Another approach would be to use Data Call-In notices (DCIs) under FIFRA section 3(c)(2)(B). Additionally, EPA is also proposing a new approach for how EPA will determine on a case-by-case basis whether a nanoscale active or inert ingredient is a "new" active or inert ingredient for purposes of FIFRA and the Pesticide Registration Improvement Act (PRIA), even when an identical, **non-nanoscale form of the nanoscale ingredient is already registered for legal use**.

In the Agency's own words, the current description is not intended "to cover biological materials (e.g. DNA, RNA, proteins) or materials in their natural state (e. g. clays)." (page 35387, third column of current proposed rule).
(b) Novozymes maintains that biological substances that naturally exist at small scales , such as microorganisms or proteins (e.g. enzymes) should not be included in the EPA's definition of nanoscale material. Novozymes would like to see the nanoparticle language by strengthened by adding enzymes and microorganisms to the list of exempted examples, with the resulting read: "biological materials (e.g. DNA, RNA, ***proteins, enzymes and microorganisms***)".

Public-private partnerships: The Administration is interested in serving as a catalyst for public-private partnerships that build the bioeconomy and address important unmet needs in areas such as health, energy, agriculture, and environment.
(16) What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

Highest impact public-private partnerships related to the bioeconomy are currently in the areas of biofuels and renewable chemicals. The shared goals of these public-private partnerships could be:

- Development of feedstocks suitable for the desired end use
- Technologies to reduce the cost of producing sugars from biomass
- Development of conversion technologies which are able to utilize pentose and hexose sugars in biomass hydrolysates to produce fuels and platform chemicals

Key attributes of a successful public private partnership are:

- Government can create, through its own use or by statute, stable and significant demand for the product (biofuel or bioproduct)
- Government ensures that the regulatory framework can support introduction of the product
- All major steps in the value chain are represented among the industry partners
- Government ensures that private partners have the resources to meet project objectives
- Government establishes baseline performance and measures progress through monitoring and audits

We expect and hope that the MOU between the DOE, Navy, and USDA (related to providing diesel and jet fuel for Navy transportation needs) will develop into an effective public-private partnership. In this case, the Navy can provide a stable demand for the biofuels, the USDA can work with its constituents to provide feedstock, and the

DOE can fund optimization of conversion technology and provide loan guarantees for the biofuel production plant.

(17) What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

We see an opportunity for continued collaborations in the national centers which provide resources in genomics, such as JGI and NCBI. Using these as examples of government supporting life science research, we would comment that JGI unfortunately caters heavily to the academic community and a shift in their emphasis would be needed for them to have a more direct impact on development of biofuels and biochemicals.

The community effort to annotate the genomes is rather hit and miss and the quality of the annotations varies dramatically for organisms that are relevant for accelerating technology related to bioeconomy advancement. As an example, fungal genomes that are relevant for discovery of industrial enzymes lags far behind relative to quality of annotations for fungal genomes that are of interest to the relevant to the medical community. It appears to reflect the level of interest in a particular organism in the community at large dictates the quality of genome annotation. We recommend that an effort be made to establish dedicated groups of experts on specific protein classes which can act to pass judgment on the quality of the gene models and their annotations. For some protein classes, such as the glycoside hydrolases (GH), experts exist, and tools and analyses exist for quality curation of new genes that fall in these classes. New gene models corresponding to other protein families are not as carefully analyzed. While genome annotation can be partially automated, the process still requires a degree of human intervention, and further investments in automated annotation pipelines are necessary.

We also see an opportunity for technology breakthroughs from the three DOE-funded Bioenergy Centers (BESC, JBEI, and GLBRC). These Centers are already producing useful insights into the recalcitrance of lignocellulosic feedstocks for biofuel applications. If the goal is for these Bioenergy Centers to become true public-private partnerships, they will need to increase their efforts to solicit guidance from biofuels industry stakeholders.

Thank you for the opportunity to submit to this Request for Information regarding a national bioeconomy blueprint.

L. Val Giddings

Senior Fellow

Information Technology and Innovation Foundation (ITIF)

Submission to the Office of Science & Technology Policy on "Building a 21st Century Bioeconomy"

Before the

Office of Science & Technology Policy

The White House

Washington, DC 20006

December 6, 2011

The Information Technology & Innovation Foundation (ITIF) lauds the Administration for taking the initiative to "develop a National Bioeconomy Blueprint detailing Administration-wide steps to harness biological research innovations to address national challenges in health, food, energy, and the environment."[1]

Because of the central role life sciences innovation plays in both the U.S. and the global economy, it is imperative that this "blueprint" development process reach a successful and early conclusion. ITIF has addressed these and similar issues several times, and we incorporate some of those comments into this letter by reference.[2] But in this letter we focus, particularly, on some of the low-hanging fruit, identifying policy changes that could quickly and dramatically enhance innovation to universal benefit.

The announcement soliciting public comments seeks input on a series of questions. Perhaps the one area in which input is solicited where easy policy changes could lead to the most dramatic and rapid positive results lies in the area of regulatory reform. Bringing regulatory oversight of innovative biotechnology products more into line with the level of potential hazard assigned by scientific analysis and experience would dramatically reduce the obstacles to commercialization these new products now face in two critical areas—biomedicine and agriculture.

The challenge of crafting policies to unleash safely the potential stemming from recent innovations in biomedicine is particularly complicated. The dramatic paradigm shift being ushered in by the age of personalized genomics has "changed everything but our way of thinking."[3] The situation is, nevertheless, rich with opportunity for improved efficiencies.

In an era where a fully sequenced individual genome will cost a thousand dollars or less, and proclivities for hereditary diseases and metabolic malfunctions can be mapped and deconstructed, it is reasonable to expect that more and more medicines will be specifically developed to treat more sharply focused, and smaller patient populations and even individuals. The era is waning in which a single blockbuster drug can be expected to produce profits sufficient to support 10,000 unsuccessful drug candidates at $800 million to $1.2 billion for each success. It is imperative to find ways to reduce the costs of R&D for new therapies and treatments. Perhaps the simplest solution would be to reconfigure FDA's approach to the design of clinical trials. The current approach is rooted in brute force statistical methods dating to the 1950s and before. This model has considerable power to detect small increments in the safety and effectiveness of drugs and therapies. Its power is rooted in the use of large patient population sample sizes and rigorous double-blind testing. The disadvantage of this approach is that treating and following the clinical course of disease in large patient populations takes a great deal of time and money. This is one of the major drivers of the unsustainably high cost of new drug development. But it is not difficult to imagine a new paradigm that would decrease costs while at the same time increasing the potential for safety, efficacy, and economy.

The gene pool of *Homo sapiens* contains an enormous wealth of genetic diversity, affording our species a wide range of adaptability to different or changing environmental conditions and constraints. The biomedical consequence of this wealth of variation is that many drugs work better on some individuals than others, have differential impacts in different populations. Using this knowledge it is increasingly possible to sort patient populations into subgroups according to the heritable differences in metabolic pathways for different chemical substrates. If this is done it will be increasingly feasible to determine safety and efficacy of drugs in these selected sub populations with not just the same but with increased confidence by comparison with the classical, large sample size/brute force statistical approaches. This could reduce the need for sample sizes greatly, with concomitant savings. Part of OSTP's blueprint for FDA should be, therefore, to instruct FDA to pursue the adaptation of clinical trial experimental design to the era of personalized genomics and drug sensitivity pre-screening at the earliest possible date.

The situation with respect to agriculture is, arguably, of even more fundamental importance, inasmuch as it is the bedrock of our entire economy, society, and civilization. The ability of agriculture in the 21st century to meet the demands of a growing world population for food, feed and fibre is not, at present, assured.[4] But the potential for agricultural innovations to meet these challenges is real, and this is foreshadowed in the OSTP solicitation in two incarnations in the solicitation: in question 5, and in questions 13-15.

> Question (5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.
>
> Question (13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.
>
> Question (14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency). Show citation box.
>
> Question (15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

Perhaps the clearest example of regulatory obstacles to innovation that do nothing to improve safety while producing a major disincentive to the investment and innovation necessary to encourage a bio based economy is seen in agriculture. Regulations administered by USDA and EPA to crops and foods improved through biotechnology were promulgated under the "Coordinated Framework for Regulation of Biotechnology," announced by OSTP in 1986.[5]

While a case was made for the regulations as originally conceived, in the intervening years implementation has clearly strayed from the original vision. Experience has shown that these biotech innovations are at least as safe as, and in many cases even safer than their conventional counterparts, which, for good reasons, generally undergo little or no regulatory scrutiny. Indeed, the brilliance of the innovations that produced these products has been recognized at the highest levels.[6] However, the gap between the degree of *a priori* regulatory scrutiny applied to these products and any legitimate basis for such scrutiny in science or experience has grown into a chasm. The time taken by USDA to provide regulatory review before these products can clear the final hurdle to commercialization has grown from approximately 110 days in the 1990s (compared to the stipulated deadline of 120 days) to 2-3 years, presently. As such, Brazil has overtaken the United States among major agricultural exporters as having the shortest time for these products in the regulatory process.[7] Although the record of safety and positive impacts from products regulated by EPA is no less impressive, EPA has recently proposed a dramatic expansion of the regulatory burden it would impose on these and related products.[8] This follows a number of recent efforts by EPA to expand its regulatory oversight into areas traditionally covered by USDA, and without any demonstrated need or justification, and no resultant increase in safety of any kind. Industry groups have registered their concerns, which have fallen on deaf ears.[9] Even more troubling, strong expressions of concern from the academic community have apparently been similarly dismissed.[10]

The harm from this regulatory irrationality can be easily identified. The U.S. Government database of "Completed Regulatory Agency Reviews" lists varieties of only 20 crops that have been approved for commercialization.[11] This category is enriched for crops grown on large acreages and for global, commodity markets (14 of 20) and contrasts dramatically with the wide range of crops being pursued in

innovative R&D in past years, when as many as 60 different crops were reflected.[12] Reviews of global R&D pipelines provide further corroboration of the erosion of the once uncontested U.S. lead in this area, as fully half of the innovations in new agricultural biotech varieties expected over the next few years are expected to come from research taking place now in other countries.[13] It is widely recognized, particularly among academic researchers that this is in no small part due to the difficulties they face in securing the necessary regulatory clearance from regulators.[14] What is to be done?

If the Administration is serious in its intent to encourage research and development essential to building a sustainable, bio-based economy, it must provide regulatory agencies with political leadership that will bring this to pass. Instead of increasing the regulatory burdens faced by innovators in this sphere, regulations that do not address credible hazards must be retired, and regulatory oversight must be refocused on areas where risks might in fact reside or significant uncertainty remains. This Administration has yet to provide such guidance, despite announcements of that intent.[15] But announcements alone do not provide a sound foundation for sustainable economic growth. Specific, concrete remedies for these problems have been identified. However, until these and similar steps are taken the vision animating OSTP's efforts to develop the blueprint they seek will remain unfulfilled.[16] Among the highest priority actions OSTP should direct be taken are these:

1. Reform the U.S. regulatory system. Regulations must be based in science and should be frequently updated to take into account the lessons gained from experience. The system should not seek zero risk as this is unattainable in the real world. Regulatory review should seek to establish that novel products are as safe as others in the marketplace. In making this evaluation regulators must take into account both the harms caused by present practices as well as opportunity costs, the potential benefits that would be lost by non-adoption. The degree of regulation should be commensurate with real risks and harms. Specifically:
2. The trigger for regulatory review should be the novelty of the introduced trait (introduced by whatever method) and not the process used to introduce the trait. The degree of scrutiny should depend on the relative risk associated with the phenotype and the host when it can be shown that the methods used do not add to the risk. The system should have clear guidelines that quantitatively specify timely decision making.
3. Exempt phenotypes from regulatory review if they could be accomplished through classical breeding methods. If a phenotype comparable to that under review could be produced by a variety of production methodologies (classical breeding vs. recombinant DNA modifications, for example) then there should be a strong presumption against any review process that would make it more difficult, for example, to see the rDNA product move into the field for R&D or commercial purposes.
4. Regulatory agencies must stop treating gene flow as intrinsically hazardous, and shift their focus to appropriate risk management/mitigation in the rare cases where genes so disseminated could, in fact, present a genuine hazard. Agencies must recognize that gene flow is a natural phenomenon and is nearly always irrelevant to safety. The potential for gene movement via pollen flow is a not, ipso facto, a cause for concern or regulatory intervention.
5. Shift to phenotype-based regulatory triggers. Agencies should transition from an event-based regulatory process to a phenotype-based process, as the hazard of a phenotype that is stably inherited has more to do with the distinguishing features of the phenotype than with the precise details of the process through which it was produced.
6. Enhance effectiveness, adaptability, and public confidence by accelerating regulatory updates and transparency. To unleash this technology and enable it to proceed at a pace dictated by the rate of scientific advance the remedy is simple: the new administration should insist on transparency and require prompt publication of proposed policy documents and regulatory guidance by responsible agencies, which must then be tasked with timely responses to public comment. This will

galvanize innovation not only in the animal biotech sector, which has suffered acutely in this regard, but broadly.

Regulators responsible for reviewing products of agricultural biotechnology today spend the vast majority of their time asking questions to which no conceivable answer could have any scientifically defensible impact on a decision for or against approval. This must not continue.

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December 6, 2011

Office of Science and Technology
Request for Information: Building A 21st Century Bioeconomy
bioeconomy@ostp.gov

The undersigned agriculture associations appreciate the opportunity to submit comments as the Office of Science and Technology prioritizes approaches to building the U.S. bioeconomy. America's agricultural producers are taking on new roles. As technology evolves, farming operations do, too. Meeting demand, improving processes, and minimizing environmental impacts are what make modern agriculture a dynamic industry. Each of our organizations has a strong interest in the availability of new technology to enhance the sustainability, productivity, and competitiveness of U.S. agriculture. In developing a blueprint for the bioeconomy, it is imperative that the U.S. agriculture industry continues to lead the way with innovation, product development and acceptance of biotechnology crops.

Within each broad category below, numbers correspond to the specific questions proposed in the Request for Information.

Grand challenges

1. The United Nations estimates that the world population will reach 9.3 billion people by 2050. With only three percent of the Earth's surface suitable for food production, there will be intensified pressure for farmers to feed, fuel and clothe a growing population using the same amount of land with fewer energy and water resources. Biotechnology is imperative to tackling such monumental challenges.

   Plant biotechnology has provided numerous benefits to U.S. agriculture including production gains that enhance global food security. Biotechnology crops have improved the ability of producers to meet market demand, both domestic and international, while supporting their rural economies. Furthermore, production efficiencies gained by utilizing biotechnology crops have resulted in higher yields, more efficient use of cropland, reduced labor and reduced crop rotation requirements.

   In the words of Dr. Norman Borlaug, "civilization as it is known today could not have evolved, nor can it survive, without an adequate food supply." American agriculture has long been at the forefront of meeting the world's ever-expanding needs for food, feed and fiber. The availability of corn, cotton, soybeans, sugarbeets, canola, alfalfa, and other crops enhanced through biotechnology will continue to assist the U.S. farmer in providing for the world's growing population. The development and adoption of these products, and the promise of new products, make possible the continued availability of agricultural goods to consumers in the U.S. and worldwide.

   An example of the future potential for biotechnology is wheat. According to the Food and Agriculture Organization of the United Nations, 20 percent of the calories consumed by the human race are derived from wheat. In recent years, droughts in Russia and Australia made global supplies uncertain, and this year U.S. farmers in some states experienced drought while other states were plagued by flooding. Innovation will be the key to the United States' ability to improve wheat production, keep up with a growing global population and adapt to changing climatic conditions around the world.

Reducing regulatory barriers to the bioeconomy

13. The United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) is refining regulations to assist in constructing defensible permitting and deregulation decisions in anticipation of legal challenges under the National Environmental Policy Act (NEPA) and other non-agricultural statutes. To date, legal challenges to APHIS decisions have been based almost exclusively on procedural grounds. As interveners or parties in many of these cases, our organizations understand that litigation, not based on human health and environmental safety, attempting to reverse APHIS's field trial and deregulation decisions is costly and troubling. Legal costs, including the adverse effects of injunctions, are an unnecessary drain on the resources of the federal government, growers, commodity organizations, and biotechnology companies.

    Legal decisions not based on science put the United States at risk of not being able to capitalize on the opportunities and benefits provided by biotechnology. The time and resources expended to litigate needless legal challenges has been debilitating to USDA's efforts to review and approve new products.

14. With more than 20 new plant biotechnology traits awaiting a regulatory decision, it is essential that APHIS continue its scientifically-sound and predictable safety-based regulatory process. We appreciate and support the role of the USDA in regulating plant pest risks under the Coordinated Framework for Regulation of Biotechnology (Coordinated Framework). As part of the National Bioeconomy Blueprint, we urge USDA to strengthen the Coordinated Framework, while maintaining the key principles and scientific rigor that have been the hallmark of the U.S. regulatory process for products of biotechnology since 1986. As APHIS continues revisions to Part 340 regulations that guide permitting and deregulation decisions for products derived from biotechnology, we stress the importance of transparency, public involvement, and rigorous safety oversight. Amended regulations should continue to be based on safety and sound science, as provided by the Plant Protection Act. Reviews should be product-based, not process-based. Marketing decisions should not be a factor in safety assessments of products derived from biotechnology.

    All previous permitting and deregulation decisions under the existing Part 340 regulation should be maintained, unless new information becomes available that requires APHIS to revisit a specific decision. We recognize there is a possibility that new information may come to light that provides a scientifically valid basis for regulation of a previously deregulated plant or organism. In such a case, the federal government has the authority to take appropriate action for that organism.

    We also support the goal of enhanced recordkeeping requirements to facilitate the agency's compliance and enforcement activities under the Plant Protection Act. Recordkeeping requirements for new permitting applications have improved significantly in the last several years. Going forward, it is important to ensure that all such requirements are justified and correspond with risk. Unnecessarily burdensome recordkeeping requirements can result in needless regulatory delays for categories of products being reviewed for field tests or deregulation.

Additional Information Relevant to the Development of the National Bioeconomy Blueprint

Our organizations have a strong interest in the continued coexistence of different cropping systems to facilitate grower and consumer choice without undermining the exceptional record of innovation,

productivity, and product stewardship in U.S. agriculture. The broader debate over the coexistence of commercialized biotech and non-biotech agricultural products can, and should, remain constructive.

We urge the administration to maintain a perspective on the contribution of production agriculture to the U.S. economy, the history of different agricultural production practices, and the interest in continued access to scientifically sound and safe technologies. In 2010, more than 50 percent of production cropland in the U.S. was planted with seed developed with modern biotechnology. Over the same period that modern biotechnology was commercialized, organic and other identity-preserved, non-biotech markets, though they remain relatively small based on consumer demand, have prospered and enjoyed steady growth. Different agriculture cropping systems have been successfully practiced in close proximity for decades.

Summary

As stakeholders in the development, deregulation and commercialization of biotechnology crops, the actions taken by government agencies on these crops have a direct impact on timely access to future traits now under development. In reviewing stakeholder comments and ultimately crafting the National Bioeconomy Blueprint, we urge the administration to maintain the integrity of the regulatory process with respect to biotechnology crops. We look forward to working with you to ensure commonsense approaches that allow for availability and future development and adoption of these tools to meet the food, fuel and fiber demands of our expanding population.

National Council of Farmer Cooperatives
National Corn Growers Association
American Farm Bureau Federation
National Association of Wheat Growers

Drexel
UNIVERSITY
Office of Research

December 6, 2011

To Whom It May Concern:

Drexel University is pleased to submit a response to the request for input on a National Bioeconomy Blueprint. This response suggests a novel bioeconomy thrust, in quite brief form, primarily because the idea is quite unconventional. We believe its merit will be to stimulate thought in this or a related direction, rather than to provide the type detailed blueprint that would be useful for more conventional approaches.

Our proposal is to develop the ability to grow biological structures for engineering applications. We propose merging the developments of modern biology with needs of classical engineering of structures to develop a means to *grow* structures rather than simply building them. Nature is adept in this domain, growing the requisite mechanical structures for flora and fauna alike. Such materials can be easily competitive with man made products in terms of salient physical properties. For example, Young's modulus for polypropylene is comparable to that for microtubules, which spontaneous assemble in living cells. Young's modulus for tooth enamel is greater than that of aluminum.

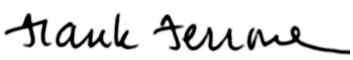
Current bioengineering efforts have been focused on highly functional elements, such as regeneration of kidneys, nerves, etc., and these deal with important problems of disease. However, we would contend that similar efforts could yield structural elements, as well as the functional ones presently sought. Indeed, nano-scale structures that can self-assemble have been a recent topic of intense study. The thrust we are proposing differs from such nanotechnology in the use of biological machinery to generate the ingredients, and biological "standards" to control the interaction. We contend therefore that our current array of bio and nano tools can be improved upon and directed toward such tasks. This could occur at many scales. For example, replacement of simple plastic panels with bio-material at "consumer scale" could occur. One could also imagine larger "industrial scale" construction.

Certain significant technical hurdles are evident, such as the genetic programming that is necessary. Yet a concerted national effort would be likely to be highly productive. Moreover, because the materials to be constructed do not involve human subjects, the protection mechanisms for research in that domain are not required, simplifying the process. Advances in this direction would necessitate deeper understanding of the biomechanics of the structural elements that would be produced in this fashion. A modern engineer knows the properties of the materials used, but if these are assembled from biological material, there must be a priori ability to understand how strong a given "grown structure" would be. The enterprise needed to develop this technology would generate significant spinoffs.

Retraining certain parts our educational system and workforce would be necessary. Working with this grand challenge will require engineers becoming adept at molecular biology without loss of their engineering competence. This therefore mandates a rethinking and reconfiguration of engineering training.

Were such a program to become productive and viable, it would clearly spawn new types of biotech industries, where biomaterials replace man-made materials. Such an industry would likely be quite "green", using biomaterials for its resources. We thus believe that, because of the various merits described above, such bio-structural engineering could become a viable element in the bioeconomy of the future.

Sincerely,



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December 6, 2011

Mr. Ted Wackler
Deputy Chief of Staff
Office of Science and Technology Policy
The White House
Delivered to: *bioeconomy@ostp.gov*

Dear Mr. Wackler,

Thank you for the opportunity to share, on behalf of my colleagues in Life Technologies, our thoughts on the National Bioeconomy Blueprint. We commend you for undertaking this initiative and for highlighting the importance of the Bioeconomy.

Life Technologies (NASDAQ: LIFE) is a leading global biotechnology tools company dedicated to improving the human condition. Our products, including cutting-edge instruments such as high-throughput DNA sequencers, are used to make life-saving biomedical research breakthroughs, to advance personalized medicine and regenerative science, to enhance food and water safety, and to solve and prevent crime with 21st century forensics. Our company's history attests to the rapid growth and evolution of the Bioeconomy. Twenty years ago we were a small company focused almost exclusively on supporting and enabling biomedical research. Today, we have annual sales of nearly $3.5 billion, over 9000 employees, and thriving businesses applying our biological knowhow to criminal justice, energy, the environment, food safety, animal health, and more. A recent report from Battelle highlights the vast reach genomics is having across multiple industry sectors already, even though the genomics revolution has just begun.[1]

[1] Battelle Technology Partnership Practice, *Economic Impact of the Human Genome Project*, http://www.battelle.org/publications/humangenomeproject.pdf.

We would also like to recognize the efforts the Administration has already taken to support the Bioeconomy. Your unflagging support for the National Institutes of Health (NIH) and science funding generally has been instrumental to driving the Bioeconomy, and will only grow in importance during these difficult economic times. Your work to expand biology based efforts in other agencies and departments is forward-thinking and provides the seeds for further growth in the life sciences. And interesting and important projects like the NIH-DARPA effort to develop integrated microphysiological systems for drug efficacy and toxicity testing move the field forward, faster.

Bioeconomy Barriers

You asked for input on roadblocks to achieving the full potential of the Bioeconomy. Outdated regulatory frameworks and processes are a drag on the bioeconomy. One of the most important steps the Administration can take to propel this sector is to timely adapt the regulatory environment to technological evolution. Our experience is that the record to date is mixed. Three examples illustrate the point:

- **Regulatory Pathway for Next Generation Sequencing**. Research and clinical trials using Next Generation Sequencing (NGS) are already showing how powerful the tool could be in human health care.[2] The Food and Drug Administration (FDA) has been working effectively with

[2] Matthew N. Bainbridge et al, "Whole-Genome Sequencing for Optimized Patient Management," *Science Translational Medicine* 3, no. 87 (2011), 1-6.

"Results of First Whole-Genome Sequencing Clinical Trial for Triple-Negative Breast Cancer Patients Will Be Presented at 2011 CTRC-AACR San Antonio Breast Cancer Symposium," *Life Technologies*, 1 December 2011, http://www.lifetechnologies.com/us/en/home/about-us/news-gallery/press-releases/2011/results-of-first-whole-geome-sequecig-cliical-trial-for-triple-e.html.

stakeholders and providers of NGS systems to understand the technology and to shape a nimble regulatory pathway that will allow disparate and rapidly evolving systems to be cleared in a timely way. Such a pathway is absolutely essential if NGS is to reach its scientific and economic potential, and the effort to date is to be commended.

FDA is taking steps toward elucidating that pathway by working closely with industry to identify a set of standards, methods, and quality metrics that both industry and end-users could access. Standardized, well characterized reference materials and methods for validation are critical. There are existing reference standards and collections within government, such as the Genetic Testing Reference Materials Coordination Program (or GeT-RM) at CDC, and the Standard Reference Materials held by NIST, as well as reference materials and controls provided or certified by CAP and other stakeholder groups. Recommendations for validation are being written by organizations like the Clinical Laboratories Standards Institutes, the Association for Molecular Pathology and others. FDA would be well-served to build on this knowledge base rather than constructing a collection and set of methods from scratch. Finally, a platform-independent clinical grade variant database would complete the collection and advance the field.

- **Draft FDA Guidance on Research Use Only/Investigational Use Only (RUO/IUO) products.** While much of this June 2011 draft guidance is non-controversial, there are provisions in it that would impose inappropriate and burdensome requirements on manufacturers of RUO/IUO products. Full enforcement of this draft guidance will cut off the supply of equipment and reagents used in many Laboratory Developed Tests, jeopardizing patient access to newborn metabolic screening and various personalized medicine diagnostics. Despite concerns raised in formal comments to the FDA by hospitals, universities,

manufacturers, patients, public health labs, and others that provisions of the guidance are dangerous, on questionable legal ground, and unwarranted by any evidence of harm, the FDA has signaled its intention to proceed to final guidance with few if any changes. The result is a drag on innovation with no obvious public or private benefit. The imposition of these onerous new requirements through a Q&A style draft guidance document that contains novel legal frameworks, in violation of FDA's own Good Guidance Practices, adds to stakeholders' frustration. This guidance should be significantly revised.

- **Veterinary Biologics.** In the veterinary biologics arena, an outdated USDA post-market batch release authorization process for USDA-CVB licensed veterinary diagnostic test kits causes significant delays and unnecessary expense. Currently, USDA's Center for Veterinary Biologics (CVB) requires that two kits from every serial that may be selected for testing must be sent in, and that two kits from every marketed serial that may be called upon during CVB investigations be retained. A batch cannot be released until CVB provides a release authorization, which can take one to three weeks. Instead, CVB should rely on manufacturer quality systems to ensure that nonconforming product does not enter into commerce. This can be done via records review during periodic inspections, as is done for many products regulated by USDA and FDA. Serious violations could result in CVB pulling a firm's license, which should ensure compliance with quality systems. CVB could and should place the burden on manufacturer quality systems not to release nonconforming product, rather than conducting the testing itself.

There are other basic ways in which our joint potential is constrained. The terms and conditions of grant programs that seek private sector participation are often a deterrent to commercial participation. For example, recently the Department of Energy (DOE) released a solicitation seeking ideas and

projects for deploying green manufacturing processes. We had an idea for replacing a toxic solvent in our processes with a plant-based one. Unfortunately, under the (common) terms of the RFP, applicants were required to provide indirect cost and fringe benefit data that we either do not keep or are not able to make public. As a result, we did not participate. The bioeconomy is filled with companies unaccustomed to government contracting and without government accounting infrastructures. Basic grant program terms can cause companies to withdraw from public private partnerships and otherwise attractive grant programs. An awareness of this type of potential structural impediment when developing programs could generate increased private participation.

Research Priorities

With respect to research priorities, we encourage the Administration to continue its strong support for the NIH. A recent report from United for Medical Research quantifies the enormous impact NIH funding has on US employment and on the international competitiveness of the US medical innovation industry.[3] As described below, two other research areas that can provide a lift to the bioeconomy include synthetic biology and the application of genomics to public health.

Synthetic Biology. Using bioengineering to design living systems holds the promise of new health care and alternative energy products, as well as the creation of new research tools. Synthetic biology research takes place in many agencies and departments within the federal government. A cross-agency and coordinated research agenda, developed in consultation with the private sector, would support advances in synthetic biology and ensure progress.

[3] Everett Ehrlich, *An Economic Engine: NIH Research, Employment, and the Future of the Medical Innovation Sector*, http://www.unitedformedicalresearch.com/wp-content/uploads/2011/08/UMR_An-Economic-Engine.pdf.

Development, validation and categorization of tools for scaled DNA construction and engineering will make the essential suite of parts and technologies available “off the shelf,” including new model organisms, chemistries, and genomics. Identification and characterization of novel hosts and properties could be followed by methods to grow and manipulate hosts more effectively and characterize their metabolism in detail.

A large stable of synthetic biology parts will require naming conventions to form a metagenomic "catalogue" of tools. Validated methods and standards for characterization, annotation, homology and domain criteria will support collaboration and comparability while reducing confusion as will development of software for genetic circuit design and function, as well as chassis context design and modeling. This working parts library could then be extended from model organisms into hosts of industrial importance.

Finally, increased computational abilities are critical for the development of synthetic biology. “In silico” capabilities, such as development of CAD and simulation software tools for genetic circuit design and function and computational methods for de novo parts design will enable bottom up de novo genome/organism design. While the private sector intends to fully participate in these efforts, government support, coordination and partnership will enable the field to progress rapidly.

Genomics and Public Health. As high throughput nucleic acid sequencing becomes more powerful and less expensive, it can be used in a wider range of applications to answer questions previously out of reach. We propose two broad applications of genomic technologies be prioritized to address the important impact of microbes on human health and disease.

According to data from the Centers for Disease Control and Prevention (CDC), food-borne illness costs the United States $150 billion per year – a major challenge to public health. Preventing outbreaks, or even shortening their duration and spread will have a significant impact on the cost of food-borne illness in terms of lives as well as dollars. Next generation sequencing can be used in the context of food safety or other pathogenic outbreaks as a complement to conventional epidemiology. This use of "genetic epidemiology" allows for rapid, more specific and detailed tracking and tracing of the cause of outbreaks, and is a powerful tool in investigations.

NGS facilitates whole genome typing by interrogating every base in a microbial or viral genome. This fine-scale characterization can lead to rapid, single base resolution strain tracking, leading to more sensitive detection of outbreak clusters, especially when caused by common PFGE types or serotypes. NGS also facilitates rapid development of outbreak-strain specific detection assays that can be immediately deployed for clinical, food, or environmental testing. For example, sequencing of the recent German *E. coli* O104:H4 outbreak strain with the semiconductor-based Ion Torrent system led to the rapid identification of strain-specific TaqMan assays. The declining cost and increasing power of whole genome sequencing is rapidly reaching a point where a full sequence could augment or replace PFGE fingerprinting as the primary typing method in PulseNet.

In order for NGS to become accepted as a method for routine microbial epidemiology studies, the instruments and methods need to undergo rigorous validation and standardization. This will include the development of methods and analyses that are compatible with existing typing schemes (e.g., PFGE and MLST). Similarly, there will need to be standardized methods for interpretation and reporting so that results from disparate local sites can be efficiently conglomerated at the CDC. Improved communications and

resources between CDC, FDA, and USDA on food safety will assist not only conventional epidemiology, but also the new "genetic epidemiology."

Life Technologies is pleased to be a leader in the Bioeconomy. We thank the Administration for its interest in and commitment to these issues, and we look forward to working with you.

Sincerely,

Mark Stevenson

Cc: Janet Lambert

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December 6, 2011

Comments Regarding the Request for Information: Building a 21st Century Bioeconomy (76 FR 62869, October 11, 2011)

To the Office of Science and Technology Policy:

In October, 2011, OSTP issued a Federal Register notice titled "Request for Information: Building A 21st Century Bioeconomy."[1] The comments below are in response to the questions therein on the role of regulation in and for an expanding bioeconomy (questions 13, 14, and 15).

For context, the authors of this letter are policy analysts, who for many years have focused on public policy aspects of biotechnology in general, and in particular of synthetic biology, an emerging technology that has potential to be an important driver of this coming century's bioeconomy. Dr. Friedman leads JCVI's Policy Group and is a coauthor of a 2007 report focusing on the biosecurity and biosafety aspects of synthetic biology.[2] Dr. Carter is also a policy analyst at JCVI. Mr. Rodemeyer, currently at the University of Virginia, was the Executive Director of the Pew Initiative on Food and Biotechnology from its inception in 2000 through 2005. In 2009, he authored an early review of the regulations that apply to synthetic biology for the Woodrow Wilson International Center for Scholars in 2009.[3]

The three of us are also investigators on an ongoing DOE-funded study to assess how well the current Federal regulatory framework applies to the anticipated products of synthetic biology, and to provide options for addressing any gaps or shortcomings. This two-year project will include two workshops as well as multiple consultations with experts both within and outside the Federal government. A full report should be available by late 2012. However, though preliminary, we feel our insights to date will be helpful to OSTP's current request for information.

The 1986 Coordinated Framework for the Regulation of Biotechnology has generally been successful: the government has been able to assess products for safety and biotechnology developers have been able to move those products to market. The regulatory system has served an important role in the marketplace as well; product developers benefit from the public's trust in the government's oversight. On the other hand, as others have observed, regulatory requirements increase costs and contribute to the challenges faced by smaller companies and independent entrepreneurs.[4] Moving forward, any changes to the

[1] 76 FR 62869, Oct 11, 2011
[2] Garfinkel M, D. Endy, and G.L. Epstein. *Synthetic Genomics | Options for Governance*, The J. Craig Venter Institute, Rockville MD, 2008, 57 pp.
[3] Rodemeyer, M (2009) New Life, Old Bottles: Regulating First-Generation Products of Synthetic Biology.
[4] Pew Initiative on Food and Biotechnology and Animal and Plant Health Inspection Service (2004) Impacts of Biotech Regulation on Small Business and University Research: Possible Barriers and Potential Solutions, Washington, D.C.

regulatory system must strike an appropriate balance between minimizing risks and avoiding roadblocks to the development of beneficial new products. At the same time, the regulatory system must provide the rigor, clarity, and transparency needed for both the public and technology developers to understand, and have confidence in, the process.

The current regulatory framework has evolved over time, both as the agencies have gained experience with the products and as the technology has advanced. In 2001, CEQ and OSTP undertook an assessment of the Coordinated Framework in part to "ensure that U.S. regulations keep pace with the latest scientific and product development."[5] Given the rapid pace of scientific advancement, particularly in synthetic biology and related technologies, we believe that another such assessment is needed. We believe that our report, building on previous work by us and others, will provide a solid foundation for this review.

In our research to date, we have found areas where products developed using new biotechnologies may not be covered clearly by the current regulatory regime. We have also found areas where more clarity in the regulatory process would help create more predictability for the approval of new bio-based products. Such gaps and uncertainties lead to delays as product developers try to determine the appropriate regulatory path to take; reducing uncertainties, filling such gaps, and providing clarity are critical to reducing regulatory barriers for the bioeconomy.

We give two examples below, one addressing genetically engineered plants and the other, engineered microbes. However, given the early stage of our project, we cannot provide a comprehensive review of all issues that need resolution. And, at this early stage of research, it is still premature for us to offer options for the directions that the Federal government might take regarding regulatory policies or risk assessments.

Clarity is needed on what types of plant biotechnology products should be reviewed by USDA and which, if any, might not need to be reviewed. USDA's Animal and Plant Health Inspection Service (APHIS) has authority to assess and regulate "plant pests" and "noxious weeds." Until recently, biotechnology developers depended on techniques that incorporated sequences from known plant pests into their products, and so were regulated by APHIS based on its authority over "plant pests." However, using new technologies, product developers will increasingly avoid using plant pests to modify plants, rendering APHIS's regulatory authority inapplicable[6] [7] and thereby creating a gap in pre-market assessment.[8] [9] It remains unclear whether and to what extent APHIS will apply its

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[5] CEQ/OSTP Assessment: Case Studies of Environmental Regulation for Biotechnology (2001)

[6] USDA's decision not to regulate modified Kentucky Bluegrass: 76 FR 39812, July 7, 2011.

[7] USDA's decision not to regulate Maize altered with zinc-finger nucleases: http://168.68.1.70/foia/foia_requests//2011/Biotechnology%20and%20Regulatory%20Services%20(BRS)/11-089%20-%20Correspondence%20Concerning%20Regulatory%20Status%20of%207%20CFR%20Part%20340/11-089%20Records.pdf

[8] Kuzma J and Kokotovich A (2011) Renegotiating GM Crop Regulation. *EMBO Reports*, Volume 12, p. 883–888.

[9] "GM grass eludes outmoded USDA oversight" (2011) *Nature*, Volume 29, No. 9, p.772

authority to regulate "noxious weeds" to plant biotechnology, as was suggested in their 2008 Proposed Rule.[10] Also, EPA has previously indicated that it has the authority to regulate modified organisms under the Toxic Substances Control Act (TSCA),[11] but whether that authority could be applied to new plant products that fall out of APHIS's system remains to be seen. Given the shifting landscape, technology developers are left with some uncertainty regarding their products.

As synthetic biology techniques and applications expand, microbes will likely grow to become a major component of the bioeconomy. The regulatory system must begin to anticipate an influx of these products; EPA in particular will need the resources to meet the risk assessment needs for these technologies. For product developers, it will be helpful for EPA to generate and release guidance on the types of data that they consider necessary to conduct a risk assessment on genetically modified microbes, particularly those that have the potential for environmental release (e.g. algae used to generate biofuels). To generate this data, it is likely that experiments involving limited release of these microbes into the environment will be required. While EPA has a TSCA Environmental Release Application (TERA) process that has been used for individual products, more general guidance on appropriate precautions to take may provide clarity for product developers as they move through this process.

The Coordinated Framework has provided guidance for both the public and developers for a quarter of a century and demonstrated its ability to adapt with experience. However, new technologies and the increasing pace of technological change are likely to create challenges for the Framework. Legal gaps and questions about regulatory pathways can create uncertainty for the public and developers alike. While there are strong arguments for maintaining the basic structure of the Framework, there will be a need to review regulatory authorities to meet the challenges of new technologies, including synthetic biology. Such a reassessment inevitably involves making difficult, but extremely important, judgments about striking the appropriate balance between regulation intended to prevent harm to public health and the environment and the desire to bring beneficial and safe products to market.

We would be happy to discuss these topics further and we will keep you apprised on the status of our upcoming report on the regulatory system for synthetic biology products.

Sincerely,

Robert Friedman, Ph.D., Director for California, J. Craig Venter Institute
Sarah R. Carter, Ph.D., Policy Analyst, J. Craig Venter Institute
Michael Rodemeyer, J.D., University of Virginia

[10] Available: http://www.aphis.usda.gov/biotechnology/340/340_index.shtml
[11] CEQ/OSTP Assessment: Case Studies of Environmental Regulation for Biotechnology (2001).

ASSOCIATION OF AMERICAN UNIVERSITIES

The Association of American Universities (AAU), representing 61 leading public and private research universities, would like to thank the Office of Science and Technology Policy (OSTP) for this opportunity to provide comments on the Bioeconomy Blueprint. The 21st century is an era of unprecedented advances in the life sciences, and research universities – in partnership with federal agencies such as the National Institutes of Health (NIH), the National Science Foundation (NSF), and the Department of Energy (DOE) – are at the cutting edge of discoveries in biology and biomedicine. Genomics is transforming our approach to fields from medicine to agriculture, even as innovative partnerships between the life and physical sciences and engineering produce life-changing technologies. While AAU believes sustained, federal investment in life sciences research is critical to our nation's future, we recognize that fiscal challenges require strategic planning on how best to allocate resources. We applaud OSTP for seeking feedback from the research community to maximize our federal research investment.

AAU's responses to the Request for Information (RFI) follow. We hope that serious consideration will also be given to the comments submitted by our individual member institutions. While some of the questions lay outside the scope of our institutional perspective and expertise, and therefore were not answered, many of the issues identified have been of longstanding interest to AAU and our member institutions.

> ***Research and development:*** **R&D investments, particularly in platform technologies, can support advances in health, energy, the environment, and agriculture, and accelerate the pace of discovery in fundamental life sciences research.**
>
> **Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?**

AAU applauds the Administration for its consistent commitment to research and development and for incorporating continued federal investment in the life sciences into the Bioeconomy Blueprint. Stable and sustained funding for scientific research underpins our nation's innovation engine; research fuels the new ideas and technologies on which our economy, health, and national security depend and generates the talent base that will drive our economy forward. Indeed, the American system of research and higher education, built upon the idea of combining research with training of young scientists and engineers, has been enormously successful. This system would be impossible without federal research funding.

Clearly, our nation must reduce federal spending and address the nation's growing debt. But we must do so in a smart and strategic way. We should not compromise our future economic growth and security through deficit reduction measures that cut spending in areas, such as scientific research and education, which are critical to our nation's ability to innovate and compete. If we want our children and grandchildren to have opportunities in the future, we need to continue to make funding for scientific research and education a national priority.

In times of fiscal constraint, questions inevitably arise about the value of our research investment and it becomes easy to focus on the short-term return on investment. As OSTP develops the Bioeconomy Blueprint, we urge you not to lose sight of the unique federal role in supporting basic, curiosity-driven research. Basic, fundamental research provides the building blocks for future innovation, economic growth, and technological advancement, although its value may be difficult to assess using short-term metrics. AAU also reiterates our support for maintaining merit review as the primary system by which research funding is awarded and scientific priorities are set. Peer review has played a central role in the success of the U.S. life sciences research enterprise, setting it apart from all other nations. We acknowledge that in a limited resource environment, meritocracy becomes more difficult to sustain as reviewers are forced into an unrealistic degree of precision when choosing between highly scored proposals, and conservatism leads them to fund potentially fewer high-risk projects and fewer innovative investigators. But the funding agencies have given this issue a great deal of thought. AAU strongly recommends that OSTP seek advice from NIH and NSF on new approaches to peer review designed to foster innovative, high-risk research, such as the NIH Transformative Research Projects program.

During times of constrained budgets, federal agencies may sacrifice investments in research infrastructure. Examples include the recent decision to eliminate the National Center for Research Resources at NIH, the disestablishment of the Armed Forces Institute of Pathology, and the loss of funding for the Arabidopsis Information Resource. But shared research resources are a crucial component of basic and translational biological research. This is particularly true as the life sciences move into an era of unprecedented large-scale projects and multidisciplinary research, with the continued revolutions in genomics and computational biology.

AAU asks that the Bioeconomy Blueprint recognize the importance of developing sustainable models for federal support of research infrastructure in the life sciences. .

> ***Moving life sciences breakthroughs from lab to market:*** **It is a challenge to commercialize advances in the life sciences because of the risk, expense, and need for many years of sustained investment. The Administration is interested in steps that it can take directly, but is also interested in encouraging experimentation with new private sector-led models for funding commercialization of life sciences research.**
>
> **What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.**

Several studies in the past few years have found that the current system of university technology transfer under the Bayh-Dole Act of 1980 is working well, especially in comparison to universities' low technology transfer activities before passage of the law. These studies include an October 2010 report by the National Research Council Committee on the Management of University Intellectual Property: *Managing University Intellectual Property in the Public Interest*, National Academies Press, October, 2010, pp. 4 & 73-74. Additional reviews of university technology transfer include the 2001 report, *NIH Response to the Conference Report Request for a Plan to Ensure Taxpayers' Interests are Protected*, and the 2003 report by the President's Council of Advisors on Science and Technology, Technology Transfer of Federally Funded R&D Clearly, ***the current legal framework for university technology commercialization established by the Bayh-Dole Act of 1980 and its implementing regulations is effective and should be maintained.***

While great strides have been made in university technology transfer since the enactment of the Bayh-Dole Act, working with industry and the federal government, there is still a great deal that our universities can do to improve. In responding to the OSTP and National Economic Council's RFI concerning the commercialization of university research and proof of concept centers in May, 2010, AAU made a number of recommendations to help overcome barriers to moving new ideas from the lab to the marketplace. Below we reiterate and expand upon some of the key points we made in that response because we believe they are equally applicable here.

- ***Finding Resources to Support Commercialization by Universities:*** One of the greatest challenges in university of technology commercialization is finding funds to support the infrastructure for commercialization and technology transfer, particularly early stage (gap and proof of concept) funding for new inventions. Technology transfer imposes significant costs on universities at a time when they are already under significant financial stress due to the economy and resulting declines in state support, endowments, and donor giving.

  The intent of commercialization by universities should be to transfer technology for further development and effective application to ensure broad public access and increased social welfare. The lack of adequate institutional and/or government resources for commercialization activities, however, may have driven some university technology transfer offices (TTOs) to focus disproportionately on revenue generation as opposed to moving new knowledge into the public domain for the public good. This situation creates the wrong incentives for optimizing technology transfer. While many TTOs operate at a loss, at times, commercialization generates net revenues. However, universities should not pursue commercialization of research primarily for this purpose. Universities, government, and industry have a responsibility to find new ways of providing university technology transfer operations with necessary support so that these operations have the correct incentives to be successful in achieving their broader mission.

  To ensure that revenue generation does not drive negative behaviors that can impede technology commercialization, universities must evaluate the indicators that they use to judge the effectiveness and quality of their technology transfer and licensing operations. Indicators that have traditionally been used to measure successful commercialization efforts at universities (e.g. patents, licenses, and revenue generation) have been overused, misapplied, or are sometimes inappropriate surrogates to measure the effectiveness of efforts by universities to commercialize research. Many of our institutions are aware of these issues and are seeking to develop better measures. Our association, as well as others including the Association of University Technology Managers (AUTM), is also taking steps to develop better commercialization effectiveness measures.

- ***State Policies*** Some states forbid equity participation in companies (i.e. startups) by state institutions, while others have policies limiting involvement of faculty in such activities due to their status as state employees. There also may be tax and funding issues associated with states that can be problematic. Additionally, states may have specific policies about use of state "facilities" for commercial activities which affect public universities. We encourage the Obama Administration to work with the nation's governors to examine the impediments these laws and regulations may create for economic innovation and growth, as well as possible solutions.

- ***Conflict of Interest:*** Increased economic engagement inevitably raises the likelihood of more financial relationships between institutions and their researchers and the companies with which they engage. In fact, one gauge of the effectiveness of commercialization is the growth of such relationships. Current perceptions that such relationships are inherently suspicious or invariably lead to unmanageable conflicts of interest must be changed. Both policymakers and the public must understand that these relationships are positive and necessary for universities to achieve greater success in commercializing their research. At the same time, it is critical that as federal agencies move to regulate potential conflicts of interest, they do not put in place regulations which inadvertently discourage appropriate interactions among research faculty, universities, and industry. We understand that conflicts of interest must be closely monitored and kept in check. However, an overly strong focus on elimination, rather than management, of conflict of interest by federal agencies would produce a chilling effect on universities' willingness and ability to engage in economic development and be directly counter to the Administration's interest in increasing commercialization by universities. As purveyors of objective knowledge, universities have their own built-in interest in managing conflicts of interest, or perceptions of such conflicts, to ensure that the integrity of research findings are not compromised.

- ***Reconsider the current cap and other restrictions on the reimbursement of university administrative costs:*** To address the issue of resources and in accordance with a recommendation made by the Government Accountability Office in September 2010 (see: University Research: Policies for the Reimbursement of Indirect Costs Need to be Updated, GAO-10-937, September 8, 2010, http://www.gao.gov/new.items/d10937.pdf), we urge the government to reexamine the existing 26 percent cap on reimbursement of university administrative costs. Costs of supporting commercialization are not allowed as direct costs of research in traditional federal research grant mechanisms. Currently, some of these costs, namely patent costs and related expenses, may be charged to universities' administrative cost pools for purposes of facilities and administrative (F&A) cost reimbursement. However, since the administrative components of F&A are capped and subject to pressures to support increased costs of regulatory compliance, there is little flexibility to support other activities such as patent and other costs related to commercialization. Removing or lifting the cap would help to ease current financial pressures universities face as a result of growing compliance demands and free up resources for other areas. Additional resources could also be freed up if certain costs, such as those associated with human subject protection, were allowed to be directly charged to grants.

- ***Provide for supplemental grants to support the translation of research with a high potential for commercialization:*** The federal research agencies have recently focused on developing new translational research programs. While we believe such programs can play an important role in helping to transfer research into the marketplace, effectiveness at translating research for commercialization is not necessarily the same as translational research. Indeed, there are many good ideas with significant commercialization potential already being generated from existing and more traditional federal research programs. The problem is that researchers and universities do not have resources available to support the proof of concept work, market analysis, and mentoring needed to translate these ideas from the university laboratory to the marketplace.

To address this situation, we recommend that the Administration consider the establishment of new "Translational Supplemental Awards." These awards would be made by the major federal research agencies to support proposals jointly submitted by an existing principal investigator and the university TTO or another appropriate institutional research or technology commercialization official. These awards would be made at the tail end of federally funded awards to support next stage research for projects that show strong clinical or market potential. We believe that providing such awards would both incentivize researchers to think about the potential commercial applications of their research and help to change the culture of the federal research agencies in ways that would help facilitate the commercialization goals of the Administration.

- ***Modify the R&D tax credit:*** The Administration is already on record in support of making the existing R&D tax credit permanent, a goal we support. In addition, we encourage the Administration to seek modifications to the R&D tax credit so that it provides a greater incentive for such investments instead of penalizing companies that invest in university research by not granting them full credit for research performed outside of the company, as is currently the case.

- ***Create additional tax incentives to promote commercialization:*** We encourage the exploration of additional ways in which the tax code could be used to encourage early stage investment in university technologies and to reward companies that license university technologies. For example, tax credits or deferral of taxes for angel investors in emerging companies can help spur additional investment at a critical period in a company's development.

- ***Seek new ways to reduce or supplement the growing expenses involved in patents:*** While we realize that increasing the degree to which universities obtain patents does not necessarily result in increased commercialization, patenting costs are increasingly becoming a barrier to commercialization by universities. We recommend consideration of new methods to support such expenses, perhaps along the lines of the competitive allocation process that is currently being used in the United Kingdom. One example might be to develop a separate commercialization rate supplement based on a set of indicators of commercialization success compared to total federal research dollars received.

What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?

AAU generally supports the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, although we have been seriously concerned both about recent legislative attempts to increase the percentage set-aside for this program, as well as the lack of funding for proof of concept research to help the program succeed. We highlight this latter issue here, but our full position may be found at: http://www.aau.edu/WorkArea/DownloadAsset.aspx?id=11944 SBIR and STTR are important to helping research cross the "valley of death," but SBIR and STTR funding presumes there is already sufficient evidence that a particular research advance or technology has enough commercial value to attract further investment for commercialization. Often times, however, there is not the funding available within our universities, or from other sources, to push these technologies to this point.

We propose the development of a targeted program focused on funding earlier stage proof of concept research across research agencies and scientific disciplines. Such a program would not only help more projects cross the "valley of death," but would also help enhance the infrastructure (e.g. expertise, personnel) and facilitate the cultural change necessary for universities to better support this kind of transfer. At least two models for such a program already exist:

- The European Research Council (ERC) has just announced a new proof of concept funding initiative to help bridge the gap between ERC-funded research and the earliest stage of marketable innovations. [1] These awards will be up to around $215,000 for individual researchers, equivalent to about one percent of ERC's budget.[2]
- The Wallace H. Coulter Foundation has established Translational Research (for individual researchers) and Translational Partnership (for institutions) Awards for proof of concept research in biomedical engineering.[3] The Translational Researcher Awards are made in amounts of approximately $100,000 per year, while the university grants have duration of five years at over $500,000 per year.

A proof of concept funding award program should have several key attributes. Like the Coulter Awards, they should be focused on both individual researchers and on institutions. Both individual and institutional funding should be subject to rigorous evaluation by carefully assembled panels of local experts in translational and proof-of-concept research. Unlike traditional research awards, the award criteria should include not just scientific merit, but also a demonstrated willingness and capability of a university in engaging project management boards comprised of industry, start-up, venture capital, technical, financial, and business/market experts. Additionally, successful applicants for this funding should be required to prove:

- agility in managing translational projects stressing market-relevant milestones,
- ability to conduct rigorous oversight and management of such projects, and
- willingness to withdraw funding from projects failing to reach essential milestones so that funding can be re-allocated to projects with more potential.

As under the Coulter model, title to inventions should remain with the institution, which is free to follow its normal invention licensing policy.

We envision several ways in which such a program might be implemented:

1) *Translational Supplemental Awards*—As discussed above, Federal research agencies would make these awards to support proposals jointly submitted by an existing principal investigator and the university technology transfer office or other appropriate institutional research or technology commercialization official.
2) *Institutional Translational Center Awards*— Larger grants to universities aimed at helping them to establish a culture that promotes the acceleration of innovative ideas into the marketplace should be supported by federal agencies. We are pleased to see that the National Heart, Lung, and Blood Institute (NHLBI) has recently announced its intent to publish a new Funding Opportunity Announcement to help to foster the creation of just such centers to

[1] http://erc.europa.eu/pdf/ERC_PR_Proof_of_Concept.pdf
[2] http://news.sciencemag.org/scienceinsider/2011/03/europe-nudges-top-scientists-to.html
[3] www.whcf.org/partnership-award/overview

"…address the problems that hinder the critical, early steps necessary to translate novel scientific advances and discoveries into commercially viable diagnostics, devices, therapeutics, and tools that improve patient care and advance public health." (see: Notice of Intent to Publish a Funding Opportunity Announcement for the NHLBI Centers for Accelerated Innovations, NOT-HL-11-157, NIH Guide). We believe that the model that is being established by the NHLBI has great potential to significantly accelerate commercialization and should be replicated by other NIH Institutes.

3) *Modification of SBIR/STTR Program*—The SBIR/STTR program could be modified in a way that would provide agencies with flexibility to use a certain proportion of funds set aside for SBIR/STTR to directly support additional proof-of-concept work at universities; specifically, new demonstration projects that would support proof-of-concept grants to universities and their faculty members. This flexibility is aimed mainly at allowing agencies such as the National Institutes of Health (NIH) and NSF to devote a proportion of their STTR funds for even earlier stage proof-of-concept research or prototype development research, the type of research that is best conducted in the settings where discoveries and innovations perceived to have commercial application are first developed, as opposed to later stage product development or for more applied pre-commercial research.

4) *Built into new programs*—For example, the new Cures Acceleration Network within the proposed NIH National Center for Advancing Translational Sciences might consider this model in developing its strategies and programs.

In summary, as the federal government focuses on facilitating the movement of basic research discoveries into the private sector, we urge that attention be paid to the need for early-stage proof-of-concept research at universities. Such research will better prepare discoveries to move effectively and efficiently into the marketplace, as well as providing universities and individual investigators with the resources to more fully incorporate considerations of commercial viability into their research enterprise.

Workforce development: **Investment in education and training is essential to creating a technically-skilled 21st century American bioeconomy workforce.**

The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

AAU recently submitted extensive comments to the NIH Working Group on the Future of the Biomedical Workforce on the topic of life sciences training and career opportunities, which may be found here: http://www.aau.edu/WorkArea/DownloadAsset.aspx?id=12706 We hope that OSTP will coordinate its efforts with this group, led by Princeton President Shirley Tilghman, in considering potential modifications to training programs to better align with career opportunities in the new bioeconomy. While we recognize that the Bioeconomy Blueprint goes beyond the biomedical into broader applications of life sciences, it is an inescapable fact that the vast majority of biologists are trained at some point through NIH training mechanisms or in NIH-funded laboratories.

The stated goal of NIH-supported training is to produce independent investigators eligible and able to obtain NIH research awards. If that is, in fact, the objective of such training, one could argue that these programs are not entirely successful. Perhaps the better approach is not to try to manage supply and demand, but rather to manage expectations and redefine the measures of "success." NIH, research institutions, and faculty involved in training share in the responsibility to provide students and postdoctoral trainees with realistic assessments of future employment prospects, through provision of accurate data on employment placement, award competition, and career opportunities. All stakeholders in the biomedical research community need to work together to eliminate the stigma that any career outcome other than an R01-funded academic investigator represents failure. While it may not be NIH's role specifically to create programs that train students and postdocs for non-research or non-clinical careers, such a role may fit the broader aims of the Bioeconomy Blueprint. Thus, NIH and other agencies should ensure flexibility in training mechanisms to allow trainees to explore non-traditional careers or gain additional skills and experiences. One example might be adjusting the payback policy on National Research Service Awards (NRSAs) to expand beyond engagement in research. In addition, to provide a future foundation for evaluating the supply and demand question, the government must find a way to capture information about career outcomes on all of the trainees it supports, regardless of funding mechanism.

What roles should community colleges play in training the bioeconomy workforce of the future?

AAU works closely with other higher education associations, including the American Association of Community Colleges. As we address the challenges facing American higher education, we are fortunate to have as a foundation colleges and universities that offer an extraordinary variety of quality educational and research experiences without a centralized system that stifles educational innovation. We must take advantage of our diverse and flexible system to meet the current opportunities and challenges in the life sciences, and community colleges are an important component of our higher education enterprise.

What role should the private sector play in training future bioeconomy scientists and engineers?

Doctoral training is of great interest to AAU, as our institutions collectively award more than half of all doctoral degrees nationwide. As a general principle, AAU believes there is a strong federal interest in ensuring that enough of our most talented college graduates go on to earn doctoral degrees. If they do not, the country's innovative capacity and economic competitiveness will be weakened. Like the federal investment in basic research, the federal investment in doctoral education fills a critical gap that neither states nor industry can fill. Talented students who receive doctoral degrees are a highly mobile national resource, and state governments often are reluctant to invest in fellowships for students who might not remain in their state. Similarly, corporations may find doctoral fellowships difficult to justify when they cannot be certain that a student will join the company after attaining the degree. Furthermore, industrial support of training programs in the wake of NIH's new rules on conflicts of interest might prove difficult for universities to manage.

What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

In an April 19, 2011 letter sent to the Secretary of Commerce, over 135 university presidents and three major higher education associations, including AAU, committed to working with industry,

private foundations, venture capitalists and local, state and federal governments to promote entrepreneurship, to accelerate the technology commercialization, and to institute policies and programs that support regional economic development. A copy of this letter can be found at: http://www.aau.edu/WorkArea/DownloadAsset.aspx?id=12084

Two areas highlighted in the letter focused on promoting innovation and entrepreneurship among students and faculty. To enhance student entrepreneurship, the university presidents that signed the letter committed to:

- Build upon and expand courses aimed at teaching entrepreneurship, provide new opportunities for experiential learning, run student business plan competitions, support student clubs, and sponsor programs that put multidisciplinary student teams to work solving real world challenges.

- Create new programs and grow existing activities to encourage undergraduates, graduate students, and post-doctoral students to pursue careers as innovators and entrepreneurs.

- Develop new cross-college, cross-disciplinary programs that connect business with science, math, technology and engineering fields.

- Extend campus-based entrepreneurship programs to reach young people in underserved and low-income areas by involving community colleges in consortia for training and mentoring in innovation and entrepreneurial activities.

To encourage faculty innovation and entrepreneurship, the presidents noted that, among other things, they use financial incentives, faculty industry sabbatical leaves, campus prizes and other forms of recognition, To further promote successful faculty entrepreneurship, they committed to:

- Expand efforts to encourage, recognize and reward faculty interest in research commercialization by providing incentives and encouraging engagements with industry, entrepreneurs and venture partners.

- Create or expand programs that connect faculty and students to the resources they need: industry partners, entrepreneurial mentors, translational research and "proof-of-concept" funds, accelerator facilities and venture creation services.

- Encourage streamlining and reduction in reporting and compliance requirements, which would allow faculty to increase time spent on proposal writing and research.

The presidents also called upon the federal government to refrain from enacting policies, such as overly stringent rules on conflict of interest that would discourage faculty willingness to work with industry or to commercialize innovative new research discoveries.

We believe the ideas presented in the university presidents' letter represent reasonable and sound ideas for promoting and supporting student and faculty entrepreneurship. We would encourage the federal government and industry to find ways that they can help support universities that are making such efforts.

Reducing regulatory barriers to the bioeconomy: **As President Obama has stated, our regulatory system must ''identify and use the best, most innovative, and least burdensome tools for achieving regulatory ends'' and ''protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation.''**

What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

AAU recently joined with the Association of Public and Land-grant Universities (APLU) and the Council on Governmental Relations (COGR) in assembling a white paper on the issue of Regulatory and Financial Reform of Federal Research Policy, which was submitted to the National Research Council committee examining the future of research universities. We suggest that this white paper would be useful to OSTP in preparing the Bioeconomy Blueprint: http://www.aau.edu/WorkArea/DownloadAsset.aspx?id=11666

We firmly believe that compliance and regulatory oversight are essential to the conduct of federally-supported research. Rationalizing the federal regulatory infrastructure is essential to the health of the university-government research partnership and to the efficient and productive use of federal research funding. Research universities strongly support the objectives of accountability, transparency, and implementation of important policy and regulatory requirements. However, the current regulatory climate has become dysfunctional – regulations do not align closely with true risk, and new regulatory mandates are unfunded due to the 26-percent cap on reimbursement of administrative costs. It is a growing fiscal challenge for universities to manage unfunded mandates as institutional budgets are being reduced, administrative cost reimbursements are being suppressed, and cost-sharing requirements are increasing.

Quantifying the burdens associated with specific regulations is difficult, though we provide anecdotal information in Appendix A of the above referenced white paper. The larger issue is the accretion of regulatory burdens and the increase in overall compliance costs over time.

While we are able to identify several regulations for outright elimination, it is often difficult to isolate or object to one regulation or category of requirements. Instead, it is the proliferation of those requirements and their uneven and unsynchronized implementation across many federal agencies that create a compliance miasma. In this environment, universities are often forced to institute one agency's compliance requirements across an entire campus, even where they don't make sense, and to sift through each agency's specific rules and develop different compliance mechanisms all aimed at the same ultimate purpose.

What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

We would again refer you to the above cited white paper on regulatory reform related to university research, which details issues with inconsistent application of federal regulations. Because of this inconsistency, universities have sometimes taken an especially conservative approach to federal

regulatory compliance, in part to ensure they avoid the hefty penalties that would be levied if an Inspector General-ordered audit found them in noncompliance. This conservatism has also increased costs, with some universities even failing to take advantage of regulatory exceptions for fear of regulatory non-compliance.

The federal government needs to help universities ensure they are complying with regulations in the most efficient way possible. It also needs to assist universities in helping assess the costs associated with regulation. Finally, working with universities, a serious attempt should be made by the Federal government to better account for, track, and reduce regulatory costs. Specifically to improve transparency and predictability of the regulatory process, AAU would recommend:

- ***Harmonize regulations and information systems between agencies and statutes where reasonable and eliminate unnecessary duplication and redundancy*.** University research is funded by 25 different federal agencies, each with a unique approach to regulatory implementation. While regulations concerning areas like human subject protections, animal welfare, export controls, select agents, responsible conduct of research, and financial conflicts of interest all serve important public policy goals, unique interpretations and implementations across agencies are difficult to manage, create inefficiencies, and increase costs. Additional challenges occur when rules applicable to grants (established by OMB) are inconsistent with rules applicable to contracts (established under the Federal Acquisition Regulations Councils).

- ***Eliminate regulations which do not add value or enhance accountability***. At least two requirements, Effort Reporting and Cost Accounting Standards, neither add value nor enhance accountability. As characterized by the Federal Demonstration Project, Effort Reporting "is based on effort which is difficult to measure, provides limited internal control value, is expensive, lacks timeliness, does not focus specifically on supporting direct charges, and is confusing when all forms of remuneration are considered." Cost Accounting Standards require institutions to disclose in writing accounting policies that are already documented in other institutional systems. Both of these regulations could be eliminated without any detriment to the accountability or oversight of the research enterprise. As other valueless regulations are identified, there should be a formal process in which each can be reviewed and made eligible for elimination.

- ***Ensure that regulations are meeting their goals in terms of performance, rather than simply in terms of process***. Research universities support the objectives of implementing important policy and regulatory requirements – research institutions take their stewardship responsibilities seriously. However, when implementation of regulation is premised on overly prescriptive measures issued by agencies, and subject to audit by federal and local auditors, institutional management of regulation becomes grossly complex and expensive. "Performance-based regulatory compliance" focuses on regulatory outcomes (e.g., research animals are treated in a humane manner) rather than intermediate measurements (e.g., all holding areas must meet specific dimensions). A regulatory approach that is based on performance-based standards offers universities greater flexibility to achieve regulatory goals and results in a more rational and cost- effective regulatory infrastructure.

- ***Designate a high level official within OMB's Office of Information and Regulatory Affairs (OIRA) to serve as a Federal Ombudsman, responsible for addressing university regulatory concerns and for seeking ways to increase regulatory efficiency***. This individual should be empowered with broad responsibilities to manage and minimize regulatory burdens applicable to research universities and institutions. The Ombudsman would assist in harmonizing and streamlining federal regulations, and would also have responsibility for reviewing specific "simplification requests." Under the auspices of the National Science and Technology Council (NSTC), the Ombudsman – along with a designated representative from OSTP – should lead an interagency group charged with regularly reviewing regulations affecting research universities. This interagency group could be organized as a new subcommittee of the National Science and Technology Council (NSTC) Committee on Science, or as part of the existing Research Business Models Subcommittee. Through an application process, research universities or university associations could submit proposals to "fix" or eliminate rules that either add no value or promote inefficiency and excessive regulatory burden.

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December 6, 2011

A RAPID LEARNING SYSTEM FOR ONCOLOGY CARE

On behalf of the American Society of Clinical Oncology (ASCO), I am pleased to submit this response to the Request for Information relative to a 21st Century Bioeconomy. ASCO and its more than 31,000 members is the world's largest medical professional society devoted to the treatment and cure of cancer. Our response centers around ASCO's efforts to harness the value of health information technology (HIT) to create an oncology care delivery system that interprets the fruits of genomic science, ensures that the proper treatment is delivered to every patient every time, and learns and improves through the daily practice of medicine. In short, we intend to learn from each cancer patient to make the treatment of subsequent patients better. We will foster economic activity through this project by:

- Engaging with numerous partners in the public and private sectors
- Eliminating unnecessary intervention, thus saving hundreds of millions of dollars in unneeded health expense that can be put to use elsewhere
- Increasing necessary intervention to improve the value of oncology care
- Promoting consistency and minimizing redundancy in HIT specifications and standards, and
- Increasing the survival of cancer patients, allowing them to return to productive activities in society. It has been estimated[1] that a 20% reduction in cancer deaths would be worth ***ten trillion dollars*** to this country. Our work has the potential to facilitate, empower and move us towards these types of gains.

GRAND CHALLENGES

One of the most important challenges facing the healthcare system is the daunting task of translating what we know about oncology care today - and the pending flood of genomic information that will be here tomorrow - into actionable decisions at the clinical practitioner level.

[1] Exceptional Returns, *The Economic Value of America's Investment in Medical Research* available at www.laskerfoundation.org/media/pdf/exceptional.pdf

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We have reached a point, through the continued development of HIT and the increasing adoption of electronic medical records (EMRs), due, in part, to "meaningful use" standards promoted by the Centers for Medicare and Medicaid Services (CMS), where we can now envision harnessing the power of this technology to transform oncology care.

The need is clear. If one looks at major cancer treatment guidelines today, less than 10% of recommended cancer treatment decision can be made on the basis of rock-solid clinical research data, leaving over 90% to be made through our best thinking, case experience, and small clinical studies. Imagine a system that some have called a Rapid Learning System[2] .

Here case data is collected seamlessly on each cancer case. The data is aggregated and analyzed by the type and stage of disease, the patient's other medical conditions and treatments, the clinical outcomes as reported by the oncology team and the outcomes provided to the system directly by the patient. One will quickly be able to recognize what works best in various populations and sub-populations of cancer patients and feed that information back to oncology practices so that care decisions are improving in real-time. For the first time, oncology care will be placed on a cycle of rapid and continuous improvement and the 90% of decisions made by best consensus will be slowly and steadily replaced by empirical data.

Decision support built into the system will ensure that the key information about what is best reaches the healthcare team precisely at the point of care. Features will include knowledge resources and comprehensive support for increasingly complex and personalized clinical decisions, availability of patient-reported data in practice records, and data exchange among providers and sites of care. Automated and secure transfer of a specified data set to the RLS will allow for HIPAA-compliant quality improvement reporting, as well as other secondary data uses.

As new drugs are developed, their release into the clinic will be monitored and their use optimized for patients who, for a variety of reasons, would not have been eligible for the study that led to FDA approval. As new agents are studied, the system will alert patients and physicians as to the proper clinical trial for that particular setting. This will be increasingly critical as small sub-populations of patients with a specific molecular lesion are needed to assess a new targeted therapy. The impact on cancer genetics and genomics is discussed below.

A NATIONAL PRIORITY

Creating the Rapid Learning System for oncology care should be a major national priority. It will build on the substantial investment being made under the HITECH Act as well as the major commitment from CMS to measure "quality of care" through the Physician Quality Reporting System (PQRS). While the later may be an acceptable approach to monitoring the quality of care given in common chronic conditions such as hypertension or type II diabetes, PPQRS is woefully inadequate to monitor cancer care. The disease we term "cancer" is actually a family of diseases with 100 or more family members.

[2] Amy P. Abernethy, Lynn M. Etheredge, Patricia A. Ganz, Paul Wallace, Robert R. German, Chalapathy Neti, Peter B. Bach, and Sharon B. Murphy, *Rapid-Learning System for Cancer Care*, JCO Sep 20, 2010:4268-4274; published online on June 28, 2010; DOI:10.1200/JCO.2010.28.5478.

Within each cancer is a wide spectrum of cases, early versus late stage, aggressive versus slow progression, metastatic versus localized, and so on. There is simply no way for CMS to create enough classic performance measures to monitor the quality of cancer care in any meaningful way, yet such quality measurement is crucial. A fully electronic system that is designed to deal with massive amounts of data is what must be created. The RLS is such a system.

The RLS will be a robust and ready-made solution for quality measure reporting requirements related to federal programs (such as the EHR Incentive Program and the Physician Quality Reporting System). Federal agencies overseeing such programs will not need to build or maintain independent systems related to cancer care. Furthermore, the RLS will facilitate surveillance initiatives, such as risk evaluation and mitigation (REMS). The RLS objectives are aligned with those of other important public and private sector health care initiatives.

MOVING LIFE SCIENCES BREATHROUGHS FROM LAB TO MARKET

The $1,000 genome is fast approaching. Soon, large numbers of patients will have their cancer and normal tissue genomes sequenced and compared. How will this information be interpreted? Once a therapy is given, how will we track what happens so we can use this genetic data more effectively to learn what works and what doesn't in actual clinical practice?

The RLS in oncology will be a key component of making sure the genomic data is used appropriately and that we learn from every patient experience. The RLS will provide an extensive and nearly real-time data set for researchers, including both clinical and patient reported data. These data will far surpass existing oncology data sets.

This becomes especially important as we further elucidate the disruptions to cellular pathways that are actually causative in cancer. Before long, even a common disease like lung cancer with over 200,000 cases per year will devolve into 20 or 30 (or more) distinct molecular subtypes. Within those subtypes are early-stage and late-stage patients. Within the stages are young and old, male and female, with and without diabetes, and so on. Without having the ability to learn from EVERY patient we will not be able to have enough data to understand in the optimal therapeutic option for EACH patient.

FOSTERING BIOINNOVATION

It takes many years and hundreds of millions of dollars to develop a new cancer drug. We must find ways to make the process of drug development and testing more efficient. The RLS is an indispensable part of that process.

Consider the following scenario. A defect in a molecular pathway in colon cancer is identified and a company has produced a drug that targets the defect. But colon cancer patients must be screened with genetic testing and the small subset of patients whose cancers contain that abnormality must be identified. Once they are, the patients and their physicians must be made aware that a drug exists that might help them. The option to enroll in a clinical trial for that drug must be brought to their attention. Once the patient and the drug trial are linked up, the outcomes from the therapy, both clinically and from the patient's point of view, will need to be collected and analyzed.

Different populations of patients with the defect may respond more or less favorably based on factors outside the cancer itself (age, gender, other medical conditions, other drugs being taken, etc.). In every step of this process the RLS can be of immeasurable assistance in facilitating the testing of the new agent and doing so far more quickly and accurately than the process that exists today.

PUBLIC-PRIVATE PARTNERSHIPS

Our work will require us to build many partnerships. While we are still at the beginning of the work, talks have been held with:

Database platform/analytics companies:

- Microsoft
- Oracle
- Google
- IBM (Watson program)

Electronic health record companies:

- Varian Medical Systems
- Altos Systems
- IKnowMed (part of US Oncology)

Pharma/biotech:

- Numerous companies

Government agencies:

- Office of Science and Technology Policy
- Veterans Administration
- National Cancer Institute
- Patient Centered Outcomes Research Institute

Non-profits:

- National Comprehensive Cancer Network
- eHealth Initiative
- Komen for the Cure
- Lance Armstrong Foundation

Patient reported outcome companies:

- Patients Like me
- Healthy Circles
- WellDoc

SUMMARY

The American Society of Clinical Oncology is committed to creating a cancer care system in which information learned from every patient encounter is used to accelerate progress against cancer.

The Rapid Learning System (RLS) for Oncology is the model to achieve this vision.

As outlined above, ASCO is building a technology-enabled infrastructure that: 1) allows data routinely collected during clinical care to be integrated, analyzed, and applied to inform and improve clinical care decisions, 2) promotes patient education, empowerment, and self-management, and 3) supports timely surveillance, research and knowledge generation.

The RLS for Oncology will connect cancer patients, survivors, families, their cancer care teams, and other health care providers. ASCO-developed, evidence-based content will form the core knowledge base, which will be continually updated by real-time data aggregation and analysis. ASCO is uniquely positioned to lead such an effort:

- ASCO is a multidisciplinary professional society that includes the full spectrum of professionals who provide cancer care.
- Initiatives from ASCO are viewed by oncologists as the work of trusted peers.
- ASCO has a longstanding commitment to and engagement in quality measurement, management and improvement, and to defining functionality and data standards for oncology information technology systems.
- ASCO has a demonstrated ability to facilitate culture change in oncology practice.

Most importantly, ASCO recognizes the crucial importance of partnerships and collaborations to achieve the RLS for oncology. We are actively seeking a host of partners from the public and private sector to provide critical support for this effort. Without such support, from commercial companies, non-profits, and government agencies such as CMS, the NCI, and providers like the Veterans Administration, it will be extremely difficult for the endeavor to succeed. However, working together, we will transform oncology care for the 21st century.

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Re: Request for Information: Building a 21st Century Bioeconomy [Federal Register/Vol. 76, No. 196]

December 6, 2011

Thank you for the opportunity for *FasterCures* to comment on the National Bioeconomy Blueprint. We applaud the Administration's efforts to harness research innovations in the life sciences to address national challenges. We also agree that bolstering biomedical innovation stands to advance our nation's economic growth and competitiveness.

Within the life sciences there are many imperatives, but our response focuses on one core objective – speeding up the time it takes to get new therapies for deadly and debilitating diseases from discovery to patients.

Despite the human and financial capital flowing through our healthcare system, the fact remains that more than 100 million Americans suffer from cancer, Alzheimer's disease, diabetes, Parkinson's disease, heart disease, and others for which there are still no cures, and, in many cases, few meaningful treatment options. Be it lack of medical breakthroughs, limited resources, or restrictive policies that are stalling progress, patients are paying the price in prolonged suffering or in life or death consequences.

Over the past few decades, the United States has refined a productive framework for developing biomedical innovations and therapies and bringing them to market, but we are now at risk of losing our competitive edge. The statistics are familiar: for every 10,000 compounds discovered, only one gets approved[i], and it usually takes 14 years and upwards of $1.2 billion to reach the market[ii]. Roadblocks abound, including a dearth of funding and support for translational and early-stage clinical research, a lack of information- and data-sharing among the stakeholders, and misaligned incentives among the stakeholders. **However, we believe the tough times facing the biomedical industry are beginning to stimulate and necessitate greater collaboration, as well as an exploration of ways to share capabilities in pre-competitive areas.**

Ensuring that the right resources and tools are in place to move basic discoveries in the lab through the therapeutic pipeline is not just about saving money and creating high-skill, high-wage jobs – though it will do both. (In fact, according to a recently released Milken Institute report,

The Global Biomedical Research Industry: Preserving U.S. Leadership, the biomedical sector directly and indirectly accounts for some 5 million U.S. jobs in pharma, biotech, medical devices, research and testing.) At its core, it is about saving *lives* by saving time.

The RFI poses many provocative and important questions, but for our response, we focus on the following four:

Question #1: Identifying one or more grand challenges for the bioeconomy, and suggesting steps that would need to be taken to achieve it/them.

Question #2: Identifying federal funding priorities in research, technologies, and infrastructures that provide the foundation for the bioeconomy.

Question #16: Recommending high-impact opportunities for public-private partnerships related to the bioeconomy – including possible goals and partners.

Question #17: Recommending high impact opportunities for pre-competitive collaboration in the life sciences – including the role government should play in developing them.

Regardless what actions are taken to move the bioeconomy blueprint forward, we strongly encourage looking for opportunities to support cross-sector, cross-disciplinary collaboration within those initiatives. This emerging research paradigm is proving instrumental in speeding up the time it takes to turn discoveries into treatments and cures.

Additionally, we recommend incorporating patient and venture philanthropy groups and perspectives in developing and implementing the blueprint as much as possible. With an extensive understanding of the needs of their particular community and disease, they are a critical part of any agenda-setting process.

Question #1: Identifying one or more grand challenges for the bioeconomy, and suggesting steps that would need to be taken to achieve it/them.

There are literally thousands of different directions in which we could take this question – challenges that address unmet medical needs; high-cost, high-casualty diseases; more efficient and effective clinical trial models; etc. – but instead we'd like to focus on an issue the federal government has already put a tremendous amount of time and effort into incentivizing: the better collection and use of patient data. We believe there is an opportunity to optimize this investment to advance medical science and speed the path to cures.

From its inception, *FasterCures* has advocated for more widespread, collaborative, and effective use of patient data – particularly data derived from biospecimens and clinical encounters contained in electronic health records – for research. We have produced multiple reports on this topic, including *Think Research* in 2005, which urged health systems to consider research needs when developing or implementing EHR systems, and *Still Thinking Research: Strategies to Advance the Use of Electronic Health Records to Bridge Patient Care and Research* in 2011, which found that while much progress had been made in pushing greater adoption of EHRs in clinical care, the health IT infrastructure is still falling far short of its potential to increase understanding of disease progression and advance biomedical innovation.

One of the barriers standing in the way of research being integrated into an EHR system is the need for high-quality data that are annotated with patient outcomes and can be used for clinical, not just quality and outcomes, research purposes. We cite in *Still Thinking Research* a number of organizations that are already testing innovative models that link research and care through imaging records, biospecimens, and genomic databases with patients' electronic health records;

some examples include the Gene Partnership Project at Children's Hospital Boston; Kaiser Permanente's Research Program on Genes, Environment, and Health; and the Genetic Alliance's Biobank.

While *FasterCures* is agnostic about the disease focus of any Administration Grand Challenge, we encourage you to prioritize initiatives that address the challenges of linking large datasets and biospecimens in an intelligent way that addresses privacy concerns and advances medical discovery. While there are good models out there, they need to be scaled and replicated to reach their full potential. This would bring benefits to all researchers in all therapeutic areas, and it is an area in which the federal government can play a unique role.

In *Still Thinking Research*, we recommended that the federal government develop an initiative with pilot projects that would create medical research IT modules that could be attached (plug and play) or retrofitted to existing health data systems that were built without the capacity to accommodate research.

To ensure this initiative reaches its full potential, the federal government should consider the need to harmonize standards for collecting genomic and molecular data and integrate these into an EHR. Genetic testing is rapidly becoming part of routine medical care, and this will keep expanding. But despite the fact that nine of the top ten causes of death in the U.S. have genetic components, there is no uniform and systematic effort to build capacity for incorporating genomic and molecular data in the national electronic health IT infrastructure.

H. Steven Wiley, a biologist at the Pacific Northwest National Laboratory talked about the data deluge in a December 1 New York Times article saying "We have these giant piles of data and no way to connect them." In the same article, Isaac Ro, an analyst at Goldman Sachs noted that he believes the field of bioinformatics for genetic analysis will be one of the biggest areas of disruptive innovation in life science tools over the next few years.

Question #2: Identifying federal funding priorities in research, technologies, and infrastructures that provide the foundation for the bioeconomy.

Translational Research at the National Institutes of Health (NIH)

In recent years the NIH has acknowledged the need to enhance its commitment to translational research so that Americans will see a better return on the enormous investment of their tax dollars in the form of improved health and cures for disease. The NIH Roadmap, launched in September 2004, set many of the right goals:

- fostering more collaborative research,
- linking existing clinical research networks,
- providing core services to aid those conducting translational research, and
- supporting training and career development of physician-investigators.

At the heart of this effort is the newly proposed **National Center for Advancing Translational Sciences (NCATS),** created by Director Francis Collins to bring together under one roof many of the translational research activities that already exist at NIH, such as:

- the National Chemical Genomics Center;
- the Therapeutics for Rare and Neglected Diseases (TRND) program;
- the Rapid Access to Interventional Development (RAID) program;
- the Clinical and Translational Science Awards (CTSA) program; and
- the NIH-FDA Joint Leadership Council.

By serving as a central point of access to resources, tools and expertise related to translational medicine; NCATS will foster efficiencies in the system from which patients can benefit. For example, given its status as a neutral third party, NCATS may be able to serve as an honest broker to match compounds abandoned by industry before approval with potential new applications, facilitate the repurposing of FDA-approved drugs, and cut across institutional boundaries to address fundamental scientific and biomedical challenges regardless of disease type.

While the NIH has historically focused on unlocking the underlying questions of biology -- that is, basic research -- Dr. Collins calls NCATS "a disruptive innovation, in a good way," saying the motivation for the new Center is "the need to view the drug development pipeline as a scientific problem, ripe for experimentation and process engineering."

As we note in our report *Crossing Over the Valley of Death*, which catalogues the challenges in translational research and highlights effective efforts in this phase in the therapeutic development process, translating a basic discovery into a chemical or biological compound that is ready to be tested in humans in no simple matter. There are a number of complicated steps in between and the academic scientists who make the discoveries are not always equipped, or even interested, in translating them to the next step. **Up to 90 percent of research projects fail before they ever get tested in humans, and by industry's estimates the number may be even higher— for every 5,000 compounds tested, only 5 make it to clinical trials, and only 1 eventually receives FDA approval.**[iii]

Facing these steep odds of success, pharmaceutical companies, which typically fund later-stage clinical research, have become increasingly risk-averse and less likely to pursue truly innovative new products. Venture investors are seeking to support products in the later stages of clinical development – "more mature, de-risked investments," according to a 2010 Ernst & Young report. There are increasingly fewer sources of capital for the higher-risk, earlier stages of R&D, allowing many promising ideas to fall into the "Valley of Death."

We need to bridge the void between basic discoveries and better medicine, and the steps in between – like target validation, assay qualification, product refinement, and pre-clinical development – are necessary investments to move promising new interventions to the patient.

NCATS will provide a significant stimulus to moving ideas out of the lab and into the clinic and we fully support NIH's willingness to disrupt its own paradigm in search of better solutions. Resourcing this new center should be a federal funding priority.

Regulatory Science at the U.S. Food and Drug Administration (FDA)

Another example of a foundation for the United States bioeconomy is the Food and Drug Administration, which regulates products that represent a quarter of all consumer spending, and industries that directly employ about four million Americans. No other agency touches American lives daily in the same way, and yet, despite such enormous responsibilities, we invest in it only two cents per day per American.

Without a well-resourced and well-equipped FDA, life-altering discoveries in the lab will not make it to the patients who need them. Increased funding for FDA must be a priority, not only to ensure that the agency can continue to review new drug applications and devices, but also to support efforts to improve its capacity for **regulatory science**. This is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.

In August 2011, FDA released its strategic plan for regulatory science, which provided details on its priorities, including:

- stimulating personalized medicine programs;
- developing medical countermeasures to protect against threats to global security; and
- ensuring the agency's capability to evaluate new, innovative technologies.

Building stronger ties between NIH and FDA is an important part of this effort, as NIH often has the resources (financial and scientific) to support the kind of process science FDA needs.

Though recent progress reports have been encouraging – the agency cleared 35 first-of-a-kind prescription drugs in the last 12 months, the second-highest annual number in the past decade – without additional capacity, FDA will simply not be able to keep up with the innovation coming out of the medical research community and help bring it to the marketplace to benefit patients.

An FDA that's functioning at peak performance can spur economic growth and accelerate the process of bringing to market promising breakthroughs that can help improve the quality of life, and even save lives. Ensuring support and resources for regulatory science initiatives at FDA, and building stronger links to NIH for this purpose, should be a federal priority.

Supporting Industry Innovation

Governments and businesses around the world are taking steps to gain an edge in the life sciences through tax-based incentives, recognizing the important role of innovation in driving economic growth, and the United States must keep pace in order to remain competitive in a global market.

Research and development activities in the biomedical industry carry substantial risks of product failure and investment losses. Tax incentives can mitigate these risks and encourage innovators and investors to commit time and resources to the cause. **The United States should make its R&D investment tax credit permanent and increase it by 25 percent in addition to exploring other incentive proposals and approaches that promote greater domestic R&D investment.**

The United States can also extend and enhance its global competitive position by supporting cutting-edge areas like nanotechnology, personalized medicine, stem cell research, and regenerative medicine, all of which hold immense potential. The federal government can establish a strong and sustainable foothold in these novel technologies through:

- Targeting federal funding in these areas;
- Market creation initiatives to spur discovery and commercialization; and
- Supporting adaptive trial designs, the use of surrogate endpoints, and ensuring adequate scientific expertise at FDA and NIH.

Training the Translators

Our success in any endeavor depends on having the right people with the right skills and incentives to do the work, and nowhere is the need for developing a new "breed of scientist" more evident than in the area of translational research. Many of the obstacles to translational research can be traced to the barriers that exist between basic and clinical scientists, who typically operate in parallel non-contiguous environments. They receive different training, pursue different career paths, work in different departments in academic settings, and are housed in different buildings.

Opportunities for cross-fertilization have been engineered out of both the research and training environments, and visions for new and unique career trajectories are often dimmed by the lack of flexibility, tolerance, and resources/incentives for scientists seeking to solve real world problems.

The training need as we see it is not just about getting more people interested in pursuing the traditional career paths of physician scientists, but rather about preparing scientists to do the work needed to move the results of basic discovery through the early stages of development.

As Dr. Garret FitzGerald, Director of the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania, has written, "…to realize this potential in the form of actual therapeutics, we need investigators with a sophisticated understanding of the principles of human medicine and expertise in both basic and human pharmacology, who are capable of projecting their preclinical work across the translational divide. Such expertise in translational medicine and therapeutics has become scant in academia, industry, and the regulatory bodies."[iv]

Dr. FitzGerald recommends a number of different actions needed to build this human capital, beginning with rebranding the field to make it more appealing to young scientists, establishing desireable career structures and rewards for them, and of course providing funding mechanisms for their training. The NIH's CTSA program, with its natural focus on training, is the perfect locus for this and it is a strategic goal of the consortium; some academic institutions have begun establishing programs in translational science on their own as well, as they perceive it to be good preparation for a career in either academic research or industry.

Rebranding, funding, and modeling career paths and incentives for translational researchers should be a federal funding priority.

Question #16: What are the highest impact opportunities for public/private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

Our response to this question and the one that follows on pre-competitive collaboration are closely linked, as they are intimately related topics, so most of what we say in this section can be considered to apply to the next one as well.

We highlight a number of new models of R&D collaboration, particularly early-stage, and highlight lessons learned from them in our recent report *Trends in Translation*, which also seeks to identify broader applications of these existing models and opportunities for new collaboration mechanisms.

The high costs and high risk of medical research make effective public/private partnerships increasingly critical. While research and development have always been multi-sectoral efforts, in this era of complex science and constrained resources no one can afford to duplicate efforts, fail to learn from failures, or drop the ball on a promising compound for lack of funding or other resources.

Before the Administration prioritizes high-impact opportunities for public/private partnerships (or pre-competitive collaborations), however, we strongly believe it must consider whether it is creating an **environment** that is conducive to these activities and whether there are legal and regulatory barriers to creating a culture in which it is acceptable for the parties to work together – a cooperative system rather than an adversarial one. Here are a few areas to examine.

Conflict-of-interest (COI). Translational research can only thrive if crosstalk between basic scientists and developers is not only allowed but also encouraged. Yet in many respects we are moving backwards in this regard, with policies becoming more restrictive and applying more broadly. While public trust in the scientific process and the results of research is essential, translating the results of publicly funded research more efficiently and effectively into improved

human health is nearly impossible without building relationships and collaborations among all the entities and sectors that fund and conduct medical research. These relationships do not always represent a "conflict" of interest; they frequently represent a "convergence" of interest.

We have often heard in interviews with scientists inside and outside NIH that the agency's current ethics policy governing individual conflicts of interest has had at times a stifling effect on recruitment and retention of clinical investigators. In the view of some, it has prevented or impeded important collaborations in translational and clinical research. While there is a genuine need for clear ethics guidelines, the current policies have the potential to inhibit NIH's ability to serve national needs, by hindering collaboration between the public and private sector that is critical to bringing research findings to development.

NIH's survey of its staff in the immediate aftermath of the 2005 policy change for its own employees showed that most believed the rules were too restrictive and that they would negatively impact NIH's ability to complete its mission, along with recruitment and retention, and that NIH should have just enforced existing rules better rather than strengthening the rules.

The Administration must consider the impact of its current and any future conflict-of-interest regulations on its ability to foster effective public/private partnership.

Technology transfer. We applaud the Obama Administration's focus on accelerating the process of transferring technology from government-funded laboratories to the private sector; much can be done to make access to technology and research materials from within the NIH and from NIH-funded research at universities more transparent and user-friendly. Some of that work is already underway, with efforts such as **CTSA-IP** – a Web site that aggregates and markets technologies from academic institutions that are part of NIH's Clinical and Translational Research Awards (CTSA) network as well as NIH itself, with the goal of enhancing research activity and private partnerships across the CTSA consortium – and the Kauffman Foundation's **iBridge Network**.

But measuring success solely by the number of licenses or amount of royalty revenue generated would be a mistake. Pushing more discoveries out the door faster will not ensure more treatments to help patients (or even more jobs, if the technologies and the companies fail); this is why NIH's focus on helping move discoveries farther down the path towards proof-of-concept is so important. Consideration must be given to the metrics used to evaluate the technology transfer activities of government agencies and of academic technology transfer offices; as we all know, "you get what you measure." We need to be thinking less about patents than about productivity. Universities need to create incentives for their faculty to collaborate appropriately with industry and commercialize their discoveries; they need to change their internal metrics of success. Are there "surrogate markers" such as amount of follow-on investment leveraged, or the stage of research at which a technology is licensed, that can be brought into the equation?

Opportunity: Drug repurposing.

One area ripe for significant federal involvement in creating public/private partnerships is drug repurposing. It used to be that finding new uses for existing drugs or abandoned compounds occurred primarily through serendipity, but now the process for identifying potential "hits" is becoming more deliberate, less expensive, and faster. Strategic collaborations between the public, private, and nonprofit sectors are springing up to shepherd research efforts around abandoned compounds that might work in other diseases, and ensure the policies, processes, and resources are in place to permit their appropriate reuse.

This is an area of keen interest for Francis Collins and the NIH because the proposed NCATS could play an instrumental role, given the private sector's lack of clear incentives to do so. NIH is already pursuing such efforts through initiatives such as **The Learning Collaborative**, an effort of its Therapeutics for Rare and Neglected Diseases (TRND) program that utilizes the

infrastructure of the National Chemical Genomics Center; in a pilot project, TRND signed a cooperative research and development agreement (CRADA) with the Leukemia and Lymphoma Society and the University of Kansas Medical Center to develop an approved drug for arthritis, Auranofin, as a potential clinical therapy for a rare blood cancer. NIH is seeking an industry partner to develop the product for this use, if the project is successful.

Opportunity: Clinical trial design innovation.
A number of important and successful public/private partnerships have been developed by the nonprofit **Foundation for the NIH** that almost certainly would not exist without this trusted third-party intermediary playing the critical convening and management role. The most recent example is the highly anticipated I-SPY 2 clinical trial combining personalized medicine with a novel trial design to develop potentially life- saving new breast cancer drugs. It was carefully crafted to allow the activity of drugs to be assessed much earlier in the research process, potentially enabling drugs to be developed and approved using fewer patients, less time, and fewer resources, potentially shaving years and hundreds of millions of dollars off the process. The treatment phase of this trial will test multiple investigational drugs that are thought to target the biology of each participant's tumor. This effort brings together a number of major pharmaceutical companies with intellectual property interests to protect, a consortium of 20 academic research institutions conducting the trials, and importantly the FDA, which will need to accept the results of the trial for product approval.

The Administration should continue to target areas such as clinical trial design innovation and drug repurposing as priorities for public/private partnership.

Question #17: What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

Over the last years there has been increasing interest within the biotech and pharmaceutical industries in collaborating more across companies and sectors on pre-competitive areas of research. Even though the concept remains ill-defined - with questions about where "pre-competitive" ends and "competitive" begins, how intellectual property should be treated, and whether it is possible to create a "marketplace" that will help facilitate the exchange of pre-competitive information – such efforts are cropping up across the landscape, some initiated by government, some by patient-driven foundations, some among companies interested in supporting tools and technologies beneficial to the industry as a whole.

Interestingly, the **oil and gas industry** – a similarly capital-intensive, high-risk industry with long timeframes for R&D – has realized the importance of pre-competitive collaboration, and now almost all exploration and development is executed through or supported by consortia of competing companies and service providers, who pool data and expertise in an effort to manage downside risk; companies take a more holistic view, and understand the need for sharing data to reduce risk and price volatility. Similarly, the pharmaceutical industry needs more data-sharing and trusted third parties to help it tackle common challenges.

One such trusted third-party is the **Foundation for the NIH** (mentioned above in reference to the I-SPY 2 trial). One of its most prominent initiatives is the **Biomarkers Consortium**, created to develop and qualify promising biomarkers critical to the development of new therapies for the prevention, early detection, diagnosis, and treatment of disease. Founding members include NIH, FDA, Centers for Medicare and Medicaid Services (CMS), and the pharmaceutical and biotechnology industry trade associations; other partners include 28 for-profit companies and 35 nonprofit organizations. Despite their importance, research into biomarkers is expensive and

high-risk and often not taken on by academic or industry researchers; it benefits all and directly profits none. The Consortium has invested significant amounts of human and financial capital in building the intellectual property, data-sharing, and anti-trust frameworks necessary to make the collaboration among disparate stakeholders work. One high-profile initiative of the Consortium has been the pathbreaking **Alzheimer's Disease Neuroimaging Initiative**, which is contributing to a flood of scientific papers and studies of new drugs to slow or stop Alzheimer's.

Among the most important factors considered key to the success of the Biomarkers Consortiunm has been the involvement of FDA. Their advice and engagement on the qualification of biomarkers being studied is a "crucial incentive for sustaining the interest and engagement of pharmaceutical companies."

Biomarkers is clearly an area crying out for more pre-competitive collaboration. The **Parkinson's Progression Markers Initiative** is another example of a significant effort, in this case initiated and intermediated by a patient-driven research foundation, the Michael J. Fox Foundation for Parkinson's Research.

There are also a number of pre-competitive collaborations oriented around data generation and aggregation. **Sage Bionetworks** is a nonprofit organization founded by former industry scientists that has explicitly aims "to establish a pre-competitive position for human disease biology" – that is, to fundamentally shift the business model of disease research away from building and patenting unique disease models, and redefining what are considered "commercial assets." Its first initiative, the Sage Commons, is an information platform for integrating mega-datasets from industry, academic, and government contributors, and making them available to be used in integrative genomics analysis and building predictive computational disease models.

Another initiative by Sage, in conjunction with the Genetic Alliance and a number of pharma companies, if called the Clinical Trial Comparator Arm Partnership, which will specifically compile datasets from the non-proprietary comparator or placebo arm of clinical trials (which are not commercially sensitive intellectual property) and establish an open repository of datasets and derived disease models for use by academic and commercial researchers. A third effort, called Arch2POCM (Archipelago to Proof of Concept in Medicine), will take a step forward from these efforts to demonstrate the feasibility of a highly efficient precompetitive drug discovery effort driven by the sharing and availability of data. No intellectual property will be generated through the POCM stage.

Another significant pre-competitive collaboration is the **Structural Genomics Consortium**, a not-for-profit organization formed to determine the three dimensional structures of proteins of medical relevance, and place them in the Protein Data Bank without restriction. Based at the Universities of Toronto and Oxford and the Karolinska Institutet in Stockholm, its current funders include GSK, Eli Lilly, Pfizer, the Novartis Research Foundation, the Wellcome Trust, and Canadian granting agencies. While it has an open access policy and puts all its findings in the public domain, it is driven by the needs of drug discovery and the development of new therapies for cancer, diabetes, obesity, and psychiatric disorders.

Some of the factors for success of pre-competitive collaborations that we have observed include:

- Trusted third parties to create and manage initiatives;
- Data-sharing;
- Learning from other collaborations' data-sharing, intellectual property and anti-trust frameworks;
- A focus on the ultimate needs of therapy discovery and development - i.e. "pre-competitive" does not mean "non-competitive" or that everything is free and open;
- Engagement with FDA.

Summary of Recommendations

We at *FasterCures* encourage the Administration to look for big ideas that seek to address not only the scientific challenges of our times, but the process challenges that keep science from benefiting patients – and ultimately our economy and global competitiveness. These may not be headline-worthy efforts, but we firmly believe they are what will prove transformational.

In sum, here are our recommendations:

- Look for opportunities to support cross-sector, cross-disciplinary collaboration in all initiatives supported by the Bioeconomy Initiative, and to involve patient groups and venture philanthropies in priority-setting and implementation.
- Prioritize Grand Challenges that address the challenges of linking large datasets and biospecimens in an intelligent way that addresses privacy concerns.
- Develop an initiative with pilot projects that would create medical research IT modules which could be attached (plug and play) or retrofitted to existing health data systems that were built without the capacity to accommodate research.
- Consider the need to harmonize standards for collecting genomic and molecular data and integrating these into an EHR.
- Support translational science programs and initiatives at NIH.
- Prioritize support for regulatory science initiatives at FDA and build stronger, mutually beneficial links to NIH for this purpose.
- Rebrand, fund, and model career paths and incentives for translational researchers.
- Make the R&D tax credit permanent and increase it by 25%.
- Promote cutting-edge areas like nanotechnology, personalized medicine, and stem cell research through funding and regulatory support.
- Review federal policies in areas such as conflict-of-interest and technology transfer to ensure they support cross-sector collaboration.
- Create and engage in pre-competitive and public/private partnerships in critical areas such as biomarker research and qualification and drug repurposing.

You have raised many critical issues in this Request for Information, and we applaud you for it. These are big problems, not given to easy solutions. As is often the case in human endeavors, the most significant challenges are often not the scientific or technological ones but the behavioral and cultural ones.

We are happy to discuss these issues with you at greater length any time. Thank you again for the opportunity to respond to this important set of questions.

Sincerely,

Margaret Anderson
Executive Director
FasterCures
www.fastercures.org

FasterCures is a nonprofit, nonpartisan center of the Milken Institute dedicated to improving the medical research system so that we can speed up the time it takes to get important new medicines from discovery to patients. Through our programmatic activities, we work with many patient advocacy, venture philanthropy, and medical research organizations across the disease spectrum to improve the effectiveness and efficiency of the medical research enterprise, and transform the way we pursue, fund, and conduct medical research. Learn more about our programs.

[i] Pharmaceutical Research and Manufacturers of America (PhRMA). 2008. *Profile 2008*. Washington, DC: PhRMA

[ii] Martino, M. (2011, October 25) Collins: NIH targeting bottlenecks in drug development process. *FiercePharma*.

[iii] Pharmaceutical Research and Manufacturers of America (PhRMA). 2008. Profile 2008. Washington, DC: PhRMA.

[iv] C.Skarke, G.A. FitzGerald, Training translators for smart drug discovery. *Sci. Transl. Med.* 2, 26cm12 (2010).

Public Comment: OSTP Plan for a National Bio-Economy

We recommend that the Office of Science and Technology Policy establish "security, sustainability, and responsibility" as one of the central grand challenges in the emerging US blueprint for a national bio-economy.

By secure, we mean that the future national bio-economy must be safe from a variety of risks and vulnerabilities to critical systems that we rely on (e.g., food, health, energy) from not only military and terrorist threats but also unanticipated dynamics and normal accidents that accompany any complex system, natural disasters, etc. By sustainable, we mean a triple-bottom line calculus that insists that environmental and social sustainability are equally constitutive of the long-term success of the bio-economy and the country. By responsible, we mean that the bio-economy must accord with a democratically robust understanding of the public good, individual and family wellbeing, and thriving, economically just communities. Achieving these three goals will require careful attention from the outset of planning for the national bio-economy to two key considerations:

(1) The potential biological, social, economic, and political outcomes of the national bio-economy, including, especially, attention to the systemic, multi-dimensional, and often contested nature of both benefits and risks and their distribution across individuals and communities.
(2) The development of appropriate governance mechanisms for eliciting democratically robust perspectives on priorities, goals, and aspirations proper to a national bio-economy, which, in turn, can inform policies and parameters for defining, evaluating, and managing benefits and risks.

These dimensions of governance should not be treated as subsidiary or epiphenomenal to specific technological goals, but should be recognized as presenting a grand challenge in their own right.

Our approach reflects, in part, new convictions in science and innovation policy that focus on the ability of technological innovation to meet pressing social needs. For instance, the 2009 National Academies' report on the future of the biosciences suggests that federal investment should encourage the development of a "new biology" that "would *enunciate and address* broad and challenging *societal* problems." Importantly, this vision acknowledges that the needs of society can and should figure into science policy at its earliest stages. The effort to develop a bioeconomy blueprint reflects a similar vision.

This vision is not just one for the biosciences, but also one for governance. While the bioeconomy blueprint rightly sees the biosciences as poised to play a central role in *addressing* some societal problems, it should also acknowledge that the challenge of *enunciating* societal needs and preferences transcends the sciences. The bioeconomy blueprint should thus incorporate structures for governance that help cultivate – and are responsive to – public preferences, values and concerns. A secure, sustainable

and responsible foundation cannot be grounded on agenda-setting frameworks limited to narrowly defined technological goals. Rather, it must include diverse means for democratic engagement from the earliest stages—including finding ways to engage interested publics who might not identify as stakeholders or use traditional means of political engagement. A secure, sustainable, and responsible bioeconomy will therefore require innovations in governance to assure that uncertainties are collectively recognized, scientific aims are calibrated to public values, and (inevitable) technological failures can be transparently and responsibly handled without eliciting crises of confidence.

Over the past half century, the US has asserted itself as a leader in the global high technology economy. Yet, this development has not come without risks. As the past decade has witnessed, threats to high technology systems, from terrorist attacks, technological failures, risk mismanagement, natural disasters, and other causes, have the potential to create vast destruction and put significant numbers of human lives at risk.

In coming decades, the development of a national bio-economy will create further complexity in the socio-technological systems underpinning US economic prosperity and quality of life. This complexity will arise from a range of developments and will be systemic in character; it will pose far reaching challenges that are not circumscribed to specific domains of innovation, and thus are not amenable to incremental, technology-specific risk assessment and management. A national bio-economy, for example, will potentially further intertwine the manufacturing and agricultural systems, heightening competition for and further stressing the development of land and water resources (e.g., the development of soy and corn-based biofuels). A national bio-economy will also significantly encourage the integration of biological and engineered systems, potentially enhancing the complex dynamics of such systems, including significantly expanding the array of newly engineered organisms released into natural environments (e.g., the push for developing genetically engineered algae for the production of bio-diesel). Finally, the development of a national bio-economy will further accelerate the development of bio-based technological interventions into human and non-human biology that raise significant questions about both risks and values (e.g., human-animal chimera).

These challenges are multidimensional and far-reaching, but if anticipated and addressed in conjunction with programs of technological innovation, they can be potentially overcome. While some innovation along these lines has taken place— for example the ELSI program of the human genome project—too often such initiatives have taken the form of mitigating the downstream consequences of specific technologies, rather than building considerations of security, sustainability, and responsibility into the design and infrastructure of innovation itself. A comprehensive blueprint should integrate attention to these dimensions into the *enunciation* of societal problems and the programs of innovation initiated to address them. The more recent examples of the strategic goal of "responsible development" in the National Nanotechnology Initiative and discussions of governance alongside of research in early visions of geoengineering are thus better models than ELSI.

In its recent report, *New Directions: The Ethics of Synthetic Biology and Emerging Technology*, the Presidential Commission for the Study of Bioethical Issues suggested a strategy of "prudent vigilance" to address these concerns. While the tenor of this recommendation is correct, the Commission's specific approach falls short of what is required to ensure a secure, sustainable, and responsible 21st century bio-economy. Although the Commission highlights the values of fairness and justice and the essential role of democratic deliberation in the governance of emerging technologies, its formulation of prudent vigilance nevertheless limits democratic consideration of security, sustainability and responsibility to reactions at the late stages of such technologies.

The Commission suggests that the scientific community alone is best positioned—and therefore responsible—for identifying emerging problems of risk, and thus of science governance. However, while technical expertise is without question indispensible to the tasks of governance, it has neither the competence nor authority to single-handedly define risks and benefits on behalf of society. Asking science to assume such responsibility places an unsustainable burden upon it, and with dire consequence. Insofar as the New Biology—of which the national bio-economy blueprint is unquestionably part—is engaged in enunciating societal challenges and practicing prudent vigilance, these tasks must be undertaken in partnership with the democratic public from the earliest stages.

We have seen the consequences of neglecting governance until problems emerge, such that society can do little more than react. Where innovation has not been transparent and accountable to public values, moments of technological failure also become crises of legitimacy and public trust. Governance must be proactive, rather than reactive. We must invest up front in not only understanding the nature of the challenges facing a 21st century bio-economy but also in acting in advance to ensure that future bio-innovation is secure, sustainable, and responsible. Like green chemistry, the goal for the national bio-economy blueprint must be to *design security, sustainability, and responsibility into the institutions and products that comprise the bio-economy from the outset*. This is a task that must involve biologists, national security experts, social scientists, political and business leaders, and the public at large in defining the goals and objectives, strategies, and metrics for assessing whether the national bio-economy meets these fundamental requirements.

At times, the call for a national bio-economy blueprint has the feel of merely another push for new investments in science and technology. It is not *and must not be*. At stake is the future of the US economy and the lives and livelihoods it engenders for American citizens over the next one hundred years. Genuinely prudent vigilance requires careful attention to the inevitable failures, externalities, and unpredictable social and environmental consequences of a national bio-economy; the blueprint must incorporate architectures for appropriate action—by governments, by companies, and by publics—to ensure that the bio-economy develops in a manner that is consistent with US security, with the sustainability of the global environment, and with the fundamental values of US citizens. Attending to this grand challenge is a *practical*

necessity for realizing a bio-economy, a *strategic imperative* for achieving policy goals, and a *democratic responsibility* for meeting obligations to society.

David Guston, Co-Director, Consortium for Science, Policy & Outcomes, Arizona State University

Clark Miller, Associate Director, Consortium for Science, Policy & Outcomes, Arizona State University

J. Benjamin Hurlbut, Assistant Professor, School of Life Sciences, Arizona State University

Jason Kelly / [redacted]
Ginkgo BioWorks, Inc.
Boston, MA

Responses to numbered items in RFI.

(14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

Biology is unique in its capacity for massive scale. No other programmable substrate can operate inexpensively in varied environments at the scale of continents. Many of the most important future applications in the bioeconomy will leverage this scalability and require the release of genetically modified organisms to affect the environment *in situ.* Examples include manipulating the soil microbial community to improve the yield of food and energy crops, using microbes for environmental cleanup, deploying biological countermeasures against the spread of disease viruses or microbes, manipulating the human gut microbiome to treat disease, and more.

The regulatory framework to support the deployment of genetically modified organisms (outside of plants) lacks clarity and thus companies are currently unable to shoulder the risk of developing new organisms for these applications. Specifically, the EPA should outline the guidelines for approving the deliberate release of engineering organisms other than plants into the environment.

(16) What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

The US government has served as the risk-tolerant, first customer for many advanced technologies including microchips, airplanes, satellites, computers, networks, and many more. By playing this role, the government has bootstrapped industries that are the foundation of our modern economy. Two of the largest applications of the bioeconomy will be in energy and advanced materials and it is essential that the Department of Energy and Department of Defense take leadership roles by serving as first customers for new technologies in these areas.

The US Navy's "Green Fleet" is a laudable first step in this direction. If this effort were amplified across all branches of the military it would create significant market pull for fuel production in the bioeconomy. The Department of Energy could also establish a complement to the 772M barrel U.S. Strategic Petroleum Reserve made up entirely of domestically manufactured renewable fuels. Both the Renewable Reserve itself and the domestic energy production technologies created in its wake would be strategic assets.

Engineered organisms are capable of atomic-level precision in manufacturing and will surely yield a revolution in "smart materials". One need only compare the self-repairing properties of biological systems to the frailty of current high-performance military materials to envision the potential. The Department of Defense through agencies such as DARPA should support the development of such advanced materials and the armed forces should serve as first customers.

Additional note: The National Bioeconomy Blueprint need not include medicine.

The bioeconomy is fundamentally about manufacturing. Biology represents the ultimate manufacturing technology – it operates with atomic-level precision, is capable of stereo- and regiospecificity in chemical reactions, works efficiently in mild process conditions, and typically produces environmentally benign waste products. A commitment to the bioeconomy represents an opportunity for the U.S. to rebuild our leadership in manufacturing and reestablish a skilled manufacturing workforce.

Government support of biology research for medical applications is already mature and well served by the National Institutes of Health. While medicine will continue to be a healthy segment of the bioeconomy, it has little room for further growth. On the other hand, energy, chemicals, and materials have been impacted little to date by advances in engineering biology and there has been comparatively little government support in these areas. As we replace petroleum as our principal raw material input in the next century there is little doubt that the impact of biology as a manufacturing technology will be transformative and the economic opportunity unparalleled. Thus the largest leverage for government investment in the bioeconomy will be in non-medical applications of biology research.

Ted Wackler
Acting Chief of Staff
Office of Science and Technology Policy

Re: Request for Information: Building a 21st Century Bioeconomy

DuPont is pleased to submit these comments in response to the Office of Science and Technology Policy (OSTP) Request for Information (RFI) regarding the National Bioeconomy Blueprint. The OSTP is seeking input and recommendations for "harnessing biological research innovations to meet national challenges in health, food, energy and the environment while creating high-wage, high-skill jobs. As a science company focused on each of these areas, DuPont is uniquely situated to respond to this solicitation. We commend the Administration for its focus on these important issues, and set forth below our response and recommendations on ways to encourage and foster innovation.

About DuPont
DuPont is a science company with a 200-year legacy of innovation in a broad range of market spaces. Its vision is to create sustainable solutions essential to a better, safer, healthier life for people everywhere. Operating in approximately 90 countries, DuPont makes a difference by bringing science-powered innovations to the world aimed at tackling big challenges, including how the world will be fed, reducing dependence on fossil fuels, and keeping people and the environment safe. In 2010, DuPont had net sales of $31.5 billion and employed 67,000 people globally.

DuPont businesses are helping to lead the bioeconomy in a number of sectors through various business units that address health, food, energy and the environment.

Food Security, Agriculture and Health
A key focus for DuPont is ensuring that enough healthy, nutritious food is available for people everywhere. To that end, DuPont commits 60 percent of its research and development dollars to ensuring the world's population has enough food. From working with farmers and growers around the world to help them increase crop yields, to developing a wide range of packaging materials that enable food to be transported without spoilage, to developing more nutritious food options and ensuring food safety, DuPont works every day to contribute to food security. Examples of our products include animal science and solutions to improve the sustainability and efficiency of meat, fish and egg production; biocatalyst solutions, such as enzymes, that reduce food production costs and extend freshness.

Our agricultural businesses focus on crop protection, land management, and seed technology. Pioneer Hi-Bred is the world's leading developer and supplier of advanced plant genetics, agronomic support, and services to farmers. Pioneer seeks to increase farmer productivity and profitability, and to develop sustainable agricultural systems for people everywhere. Increasing populations, changing economies, and limited cultivatable land are significant factors driving Pioneer to use the broad application of plant science to

improve the value generated from each field.

Energy and the Environment
We are committed to reducing dependence on fossil fuels by creating cost-effective conversion of non-fossil carbon sources to high value products, products and technology for first generation ethanol and advanced biofuel production and materials and chemicals made from renewable resources.

DuPont Industrial Biosciences works with partners and customers to create world-changing solutions for a bio-based society. Industrial biotechnology holds great promise to solve global challenges, offering new potentials for meeting the world's demand for food, feed, fuel, materials and more while reducing our impact on the environment. We produce bioactives, such as enzymes, peptides and performance proteins, for markets such as food, animal nutrition, detergents, and textiles; biomaterials, such as advanced materials and intermediates manufactured with renewable feedstocks; and, biorefineries, such as products and technology for converting agricultural feedstocks into carbohydrates and fuels. We maintain a commitment to continuous evolution, ever improving our products and processes, making what used to be known as "alternative" materials into mainstream ones.

I. Grand Challenges: Global demand for more and healthier food and energy will put increasing demands on the agricultural sector.

Both food and energy security have substantial effects on our country's economy and national security. Global food demand will increase substantially in the coming decades, with a growing population expected to hit nine billion by 2050, increasingly urbanized populations, and a middle class with changing food preferences. Food shortages across the globe create political instability and disruption that can drastically impact our security at home, and the ability of our companies to do business and operate effectively abroad. Similarly, increased demands on energy supplies are driving the need for innovative solutions to reduce costs, improve efficiency and diversify energy sources.

Scientific advances in the agricultural sector have resulted in substantial gains in productivity over the years. Today, seed companies use a sophisticated toolkit, combining advances in genetics to continuously breed better germplasm for diverse conditions, and technological advances in biotechnology to incorporate new input and output traits. This results in greater yield for farmers, increased nutritional benefits to consumers, environmental sustainability by reducing nitrogen use and developing drought resistance, and better defense against threats.

Despite the scientific advances that have taken place to date in the agricultural sector, the challenge of the food, feed, fiber and fuel needs of a booming population will require much more. It will require producing more food with increased nutritional value, it will require making food more accessible and affordable for everyone, and will require doing all of this in a sustainable way given a scarcity of resources. Innovation in science will be paramount, but innovative collaborations to meet our needs will be equally as important.

Agricultural productivity and biotechnology advancements are also critical to supplying the feedstocks for materials and fuels.

To meet these challenges, we recommend the following:

- Regulatory schemes should be science-based, promote and foster innovative solutions in agricultural and industrial biotechnology. Public policy should facilitate competition in the marketplace to ensure that farmers and customers have the choice of tools and technology that are more effective at the best price.
- Investments should be made in public research and development funding in agriculture. The government should collaborate with other organizations to promote research in areas such as improvement of indigenous crops, as well as technology and best practices to improve agricultural sustainability and resource efficiency.
- Governments, companies, nonprofits and other organizations must collaborate differently and more effectively to find innovative, holistic solutions, across the entire supply chain to meet the demand for food, feed, fuel and materials, while protecting the environment and assuring everyone's access to safe, nutritious food and sustainable energy supplies.
- The federal government should work with companies and governments abroad to ensure strong intellectual property and trade secret protection.
- The government should continue to fund foreign aid and companies and organizations should support efforts to reduce uncertainty and risk in order to make long-term investments in emerging markets to enhance food security in those regions.
- Governments and the private sector should work together to ensure a skilled and globally competitive workforce and to educate society on the benefits of science and bioeconomy innovations.

The bio-based economy will use biotechnology to convert renewable raw materials derived from plants, starch, and cellulosic biomass sources into food, feed, energy and other products needed by advanced societies, while reducing our impact on the environment. Industrial bio-processes will complement and, in some cases replace, traditional chemical processes. DuPont and many others have been working on bio-based solutions for several years already, and have demonstrated that biotechnology solutions can significantly improve agriculture productivity and renewably sourced products can provide a solid foundation for continued economic growth and sustainable development.

II. Government R&D Investment and Development Support is Vital to Growth

Substantial investment by both the public and private sector are necessary to meet these challenges.

Establishing and commercializing a new technology foundation for our economy is a massive, but critical, undertaking. Government support can mitigate the risk inherent in new technologies, which require huge investments and long time horizons, and are therefore extremely difficult for any company to undertake in isolation.

In the industrial arena, the conversion to a real bio-economy focused on addressing the global food and energy challenges hinges on the control of raw material costs and conversion processes. Complementary action by government might include supporting the creation of the new raw materials supply chain - a comprehensive and coherent strategy to direct efforts in biomass development, engineering and sourcing, coupled with sponsorship of competitive processes for conversion to final products. In addition, continued support is needed for public-private research collaborations to achieve biomass density goals (development of energy crop technologies). By focusing the various academic and private resources to consolidate the raw material path and then allowing competition and diversity in the subsequent conversion steps, we will more rapidly hit the high-value and high-volume targets.

Public research and investment in basic and applied research is required to maintain U.S. competitiveness for crop production systems and industrial biotechnology applications. Encouraging U.S. students to obtain advanced science degrees (Masters and PhD) is also important to maintain a pipeline of future talent in the biosciences.

Encouraging public-private partnerships to accelerate new technology development and deployment is also important.

Limited government support through pilot and demonstration can be more valuable, given the technology risk and capital intensity required. Ranges of $25-50 million would be sufficient scale to demonstrate feasibility for the next level of financing within the private sector. Ensuring the use of market-based performance metrics (cost, capital productivity, sustainability delivered) through independent private sector review could provide a mechanism to distribute funding to the more deserving opportunities. Heavier involvement in middle-to-late stages by large industrial entities is key to drive large-scale commercialization in this sector. Many large companies have taken significant steps here, including DuPont. We have proven our ability to bring new, advanced, bio-based technology to market, with commercial products available today in our Biomaterials and Bioactives segments. We will build on this foundation as we invest about $200 million per year through 2015 to bring our advanced biofuels technology from the current demonstration plants to full commercial scale. Government support is important for the next stage to help modify the risk for bringing innovation to scale.

Later-stage government support would best facilitated by:

- Clear, stable, long-term policy signals that reduce the risk and justify investment today.
- Effective Interagency coordination to ensure consistent strategic direction and support.
- Streamlined regulatory review and approval processes better matched to private sector pace and timelines.
- Farming support programs to enable establishment of the commercial energy crop supply chain, which requires significant investment prior to completion of large-scale biorefinery projects.

- Refundable, product-based, tax credits, based upon success of operational economics and market requirements.

III. Investments in Education are Important to Make our Workforce Globally Competitive and Society Accepting of Bioeconomy Solutions

Addressing long term food and fuel challenges will require generational investment to encourage science-based education. Expanding and encouraging science and math education in primary education will be necessary to lead to a higher number of undergraduates entering secondary education science and math programs. Identifying and encouraging programs and curriculum that bring more students into bioscience majors is also important, beginning as early as kindergarten and throughout secondary school. Additionally, K-12 educational curriculum should enhance general understanding of science and how it can help address our most pressing global challenges.

Community colleges can play an important role in bringing urban-based students into educational programs that support agriculture and bioscience. Training university students at all levels to understand basic plant biotechnology principles is imperative. The private sector can play an important role in training through internships programs and programs that supplement graduate student education.

Fostering a system of science-based education will also help build a society that embraces the role of science in addressing global challenges like food and energy security and environmental protection, and accepts the innovations that come from a bioeconomy.

IV. Reducing Regulatory Barriers: A Science-Based Regulatory Environment that Encourages Competition and Innovation

To address the grand challenges of food and energy security, regulatory schemes both here and abroad should be science-based, and should promote and foster safe, innovative solutions in agricultural and industrial biotechnology. Public policy should facilitate competition in the marketplace to ensure that farmers and customers have the choice of tools and technology that are more effective at the best price.

Open and clear regulatory pathways are necessary to facilitate innovation and access in the area of agricultural traits. The first agricultural biotechnology trait patent is set to expire in 2014, with several others to follow. There is a pressing need to more clearly define the transition to generic biotechnology products and associated issues pertaining to registration, stewardship and the appropriate use of and access to data created to satisfy regulatory requirements. Currently, we have no regulatory pathway to allow for the use of biotechnology traits in the agriculture space once those traits lose their patent protection.

The U.S. patent policy provides for limited monopoly power to reward technology innovators. This limited exclusivity was never intended to permanently bar new market

entrants after a patent expires. But, that is what is happening in the newer area of agricultural biotechnology, where seed patent holders can exclude potential generic entrants by simply withholding information required to manufacture and market the seeds. In contrast, in the pharmaceutical industry, there are legal and regulatory structures in place to ensure that generic medications, which are equally valuable to treating illnesses and diseases – make it to the hands of patients in our country, giving them the choice to choose between brands and generics. Similarly, there exists a regulatory structure in the crop protection industry.

Additionally, industry and government scientists and policy makers should work on a common understanding of sound science and protective regulations. For example, regulations attempting to achieve "zero risk" can result in unnecessary testing and major delays in biotechnology product approvals.

Potential suggestions for improvement in industry/regulator dialogue could include:

- Visit production plants
- Interface with safety experts in the field (both academic and industrial).
- Convening panels to work on common definitions and standards.

V. Public/Private Partnerships are Essential to Achieve Scale

The challenges outlined above are complex and beyond the capacity of any one organization to solve. Not only will scientific advancements be required to solve these problems, DuPont believes innovation in the way organizations and governments partner and collaborate will be necessary to achieve the kind of scale and impact necessary to meet our global challenges.

A major innovation of the last century was to learn to use fossil fuel based sources for our transportation, energy, and material needs. At the turn of the 20th century, 25% of all energy used in the US came from burning wood, and in 1915, some 90 million acres of US cropland were used to grow feed for horses and mules – our transportation at that time. The objective for the next century is securing alternate and renewable sources of carbon, through the application of industrial biotechnology. DuPont believes this can be achieved in a very sustainable manner, without increasing the environmental footprint of the agricultural enterprise.

Similarly, the food security crisis will require more and different kinds of collaboration between governments, NGO, the private sector and other organizations than ever before, to achieve the research necessary to achieve better and more sustainable productivity, more funding and resources to make an impact on a larger scale, and to drive change across the entire value chain.

Government support and funding is a key driver of progress in many scientific sectors. Models that emphasize (i) focused and substantial programs aimed at a key high impact areas, (ii) clear metrics that drive company investment and participation to commercialize

by private sector, and (iii) that provide near term as well as long term visible results, would help provide confidence and ensure longer term funding and desired outcomes.

Conclusion

DuPont commends the Administration for its interest in the bioeconomy and innovation in key areas, including health, food, energy and the environment. DuPont is committed to advancing solutions in these areas through the latest science and technology, and by continuing to partner with other interested organizations. DuPont appreciates the opportunity to respond to this solicitation and stands ready to serve as a resource on these issues to federal regulators.

Bioeconomy Response

Dear Reader-

I would like to respond to the questions you posed regarding the role education institutions and private sector should play in training the future bioeconomy work force. I hold a Ph.D. in Neurobiology from the University of Chicago. I spent 14 years teaching and conducting research at a Medical School, and the past 5 years developing patents into new diagnostic tests. During my academic career I was supported, for the most part by NIH grants, and some non-GMO foundation funding. My private sector work has been funded from corporate budget, and occasionally through an SBIR.

There is a need in our laboratories for practically trained individuals who have the knowledge base needed to excel in biopharmaceutical manufacturing of regenerative therapeutics and molecular diagnostic. The necessary skills can be taught at community colleges, as well as, four-year colleges and universities. It is not necessary to have a PhD to have the skills needed.

Specific bio-manufacturing degree programs with AA, BS and MS can be established as a private/public sector collaboration, and a professional society could be encouraged to generate "board exams" that indicate varying levels of competency around cGMP manufacturing, quality control, design master files, etc.

Specific federal funding in the way of scholarship for training at community colleges, colleges and universities should be made available to help entice students into this career path. Educational institutions could apply for grants that help them build such programs if they secure matching funds from a non-GMO source.

In order to fund these programs without cutting into the strapped NIH budget I would change the how revenue from patents resulting from NIH-funded research is distributed. Currently University Research Associations, who file patents, collects the majority of the funds, and although they claim to use this money to drive innovation, I would like to see a small portion of the proceeds return to the NIH to fund training programs at the bachelors-degree level and below. The average American tax-payer has long paid to fund this research without being able to readily discern the advantage they receive. By using a portion of the royalties to fund scholarships the public would benefit more directly from NIH funding, and we would create a skilled work-force with incomes sufficient to afford the goods and services their industry produces.

This is just one idea on how provide people with good paying jobs, and improve the quality of life for all of us.

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&

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Department of Physiology

Submitted on behalf of Jennie Hunter Cevera, Ph.D., Executive Vice President, RTI International
By Patrick Gibbons, RTI International

Grand Challenge
Human Proteome and Metabolome – this is needed to advance our understanding of both wellness and the onset of disease. The Genome was only the guide, but the proteome and meabolome will decipher the how, when and why. This could also help reduce health care costs since a more rational approach to individual medicine would be an outcome.

This basic, applied and translational research program should be integrated and supported by NIH, FDA and NIST. Investments would also be made to industry to produce the new tools in the "toolbox" such as more sensitive mass spectrometry and computational analysis for complex data sets.

Focused Research
The Federal government should provide funding mechanisms for development or proof-of-concept research, as well as public-private partnerships to promote innovation and commercialization. Currently funding agencies are top heavy on basic research and lean on "team science," or applied, interdisciplinary research. Study sections often align on their agendas, rather than the funding agency roadmaps. Priority needs to be given to the research and outcomes that support agency priorities and roadmaps.
The critical technical challenges that prevent high throughput approaches from accelerating bioeconomy research include the lack of advanced analytical tools and the funding for "tool box" development. There is a need for integrated research programs that bring together physics, mathematics, biology and chemistry under one umbrella, or within a single framework. Priority should be given to exploring chemical "whispering" at the sub-cellular level and on developing "omics" and bio-imaging capabilities. These types of multidisciplinary funding efforts could revolutionize predictions of protein functions of genes.
Barriers that prevent biological research discoveries from moving from the lab to commercial markets include a lack of understanding of how and why development science and technology functions; a lack of teamwork in universities; a lack of integration on sponsored research with business development; sparse outreach interaction with industry to identify needs and research gaps; a system that promotes based on publications rather than patents; a lack of trained industry people working in universities; and the need for savvy people in the research trenches to ask the right questions about potential applications of basic research.
Increasing funding for SBIR and STTR might encourage more university and government laboratories to reach out and partner with industry. Also bringing back the ATP program at NIST would make a positive difference since these awards are larger than SBIR or STTR.
The Department of Defense does significant research resembling "biology on the edge," but it is selective in what it releases. Perhaps here is where another grand challenge could play a role by creating more public-private partnerships for drug discovery.
The challenge to existing private-sector models for financing entrepreneurial bioeconomy firms is that very few firms are willing to invest in early stage technology. Perhaps if the government offered matching funds – a kind of "grand angel" that could partner with venture firms within established parameters – then more early technologies might get past the valley of death and make it to the market.

Work Force Development

To better prepare scientists and engineers for private-sector bioeconomy jobs, universities could require internships in industry and partner more with industry on solving their problems. If government funding agencies matched industry dollars for graduate and post-doctoral fellowships to focus on moving ideas or hypotheses from concept to proof-of-concept, and on to product or process, we would have much faster returns on the investment of obtaining graduate degrees and post-doctoral fellowship experiences.

Community colleges are becoming more and more popular for high school students to attend rather than four-year degree programs. Programs that focus on "real world" or hands-on experience the entry of graduates into the workforce in industry and ensure they have the skills needed to hit the ground running, instead of requiring extensive company training. Many entry-level positions require at least a 2-year associate's degree. Absent an internship, these new employees need at least six months additional training. If there were a way to tailor community college applied technology programs to real manufacturing scenarios (mock FDA trials, etc.), it could save time and money for the biotechnology industry. Private industry could design the curriculum and training programs for students and also provide guest lecturers.

For government and industry to successfully partner with academia and encourage successful entrepreneurship by faculty, graduate students and post-doctoral students, universities will have to adjust their approach and develop a culture of entrepreneurship. They should consider embracing "team science," doing away with tenure, and moving toward performance-based promotions for faculty. Faculty members should lead, and students should follow. Change is needed to become more competitive in the global economy.

Reducing Regulatory Barriers

The FDA is woefully underfunded and has not been able to keep up with the emerging bioeconomy. Genetic tests seemingly take forever to get approved, yet they could make a huge difference in choosing the right drug for cancer, etc. Please read the Personalized Medicine Coalition's recently issued ***Case for Change*** report.

The federal government is unlikely to improve the predictability or transparency of regulatory processes until the regulatory system is overhauled and equipped with additional financial and human resources, including internships from the drug industry.

Our regulatory systems are based on many prior experiences that covered biochemistry and physiology. Today the shift is toward "omics" and sub-cellular chemistry, yet the regulatory guidelines are not well suited for the type of medicine and practice towards personalized or individualized medicine.

The FDA for years has focused on single compounds and yet the data and evidence for therapies that involve more than one compound to cure a disease is growing along with evidence associated with diet and exercise. It would be great to have a program that integrated wellness and disease research and healthy lifestyle promotion. NIH mainly focuses on disease, not on health or wellness. Perhaps it is time to create a new federal agency that focuses on wellness and well-being.

Public-Private Partnership

Some public-private partnerships have worked well in the past (TMT and Novartis). A grand challenge that unites public and private institutions in dealing with obesity in this country might make a huge impact in both the bioeconomy and the healthcare and the food industries.

Obesity causes diabetes, cancer and heart disease, which in turn leads to a less healthy workforce for America. Companies today are spending a fortune on healthcare for employees, many of

which are on high cost medication to deal with chronic diseases that could have been avoided if employees ate better and exercised. T
The bioeconomy is a two-way street: high paying jobs provide a higher tax base, but if the workforce is not healthy, it can cost companies more money and slow down productivity.

Office of Science and Technology Policy (OSTP)
Request for Information (RFI)
Federal Register Vol. 76, No. 196, October 11, 2011

Response from Spyglass Biosecurity, Inc. and Farragut Advisory Services LLC:
National Biotechnology Blueprint

The White House
Office of Science and Technology Policy
Associate Director, Science Division
Assistant Director, Biological Research
Assistant Director, Biotechnology
BIOECONOMY@OSTP.GOV

To Whom It May Concern:

Thank you very much for issuing the above-referenced Request for Information (RFI), in order to solicit input from stakeholders for the development of the Administration's National Biotechnology Blueprint.

Spyglass Biosecurity, Inc. and Farragut Advisory Services LLC are pleased to provide this response to the RFI. Spyglass Biosecurity, Inc. ("Spyglass") is an early-stage California company (a certified service-connected disabled veteran owned business) founded in 2008 by Chris Melançon to serve customers who require timely and precise information to protect and preserve water resources and enable water research. Spyglass delivers portable water laboratories with leading biology-based detection technologies that have been proven in a centralized laboratory setting and that have subsequently been automated for use in a field environment. Farragut Advisory Services LLC is a Washington, D.C.-based consultancy that assists clients in all aspects of doing business with public sector customers ("FAS LLC"). FAS LLC's Principal, Daniel Mazella, has provided thoughtful, cost-effective advice and guidance to clients for more than twenty years.

RFI Question: "Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment and agriculture, and suggest steps that would need to be taken [by stakeholders] to achieve this goal."

"Research and development: R&D investments, *particularly in platform technologies,* can support advances in health, energy, the environment, and agriculture, and accelerate the pace of discovery in fundamental life science research."

The health of our water resources is a primary indicator of the health of our planet. Water is necessary for the survival of virtually all life on Earth, but our ability to separate and analyze, identify or quantitate microbial ecosystems and harmful organisms in water has been limited because of barriers to the development and commercialization of biotechnology tools for testing.

We respectfully suggest that an appropriate "Grand Challenge" for consideration is the development and commercialization - and implementation in the field - of biotechnology tools to protect water resources.

Technology exists today that can be further developed and extended in order to effectively respond to the Grand Challenge of protecting our water resources.

Public Health: real-time monitoring of water quality using biotechnology tools and platforms can help prevent illness from water-borne pathogens, toxins and chemical contaminants. For example, emerging pathogens in drinking water can render current treatment methods inadequate; the presence of sewage in beach water (due to aging infrastructure), toxic algal blooms that cause paralytic shellfish poisoning, volatile organic chemicals (VOCs) leaching into water supplies.

Agriculture: real-time monitoring of water quality using biotechnology tools and platforms can help prevent illness from water-borne pathogens, toxins and chemical contaminants that are used for irrigation or processing of agricultural products. For example, during the past year, new strains of *E. coli* were discovered in Germany, and *Salmonella* in food caused illness and resulted in the recall of agricultural products.

Energy: Energy and water are inextricably linked. As new renewable technologies are developed and deployed, a thorough understanding the impact on aquatic ecosystems as well as water supplies is important. We suggest that the use of biotechnology tools and platforms would further scientific research in the nexus between energy and water.

Environment: Seventy five percent of the global population will live within 125 miles of a coastline by 2025. Fifty percent reside there today. We are introducing new stressors and contaminants into our water supplies. We suggest that the best way to manage that impact and respond to it effectively is to have real-time, reliable information on the health and safety of water resources.

Barriers to the Development and Commercialization of Biotechnology Tools for the Protection of Water Resources

The following are, in our view, some of the impediments to the use of biotechnology tools for testing drinking water for man-made and naturally occurring contaminants; monitoring recreational water quality; detecting invasive species; and aquaculture/agriculture pathogen monitoring:

1. Lack of reference standards for pathogen testing of water (seawater and freshwater);

2. Platform technology for the acquisition of samples and for the preparation, collection and isolation of pathogens has not been sufficiently developed and implemented;

3. Funding issues at all levels of government.

In addition, as an early stage company engaged in the development of an information network for testing of water resources, Spyglass can speak from firsthand experience in building a business that develops and commercialize a platform and assays for pathogen testing. Spyglass is faced with the challenge of in-licensing technology, further developing such technology and turning it into a set of products, and selling the products in the marketplace. As such, Spyglass can attest that the so-called "valley of death" that has been described as existing for the development and commercialization of diagnostics and therapeutics also exists for the development and commercialization of biotechnology tools and platforms for the identification of pathogens in water. Obviously, this "valley of death" in funding for the labor and research-intensive time prior to the sale of products is a barrier. Often venture capital seeks returns on investments within three to five years and so the near-term outlook disqualifies many critical technologies from the venture capital funding model.

Concrete Steps to Address the Grand Challenge:

1. Identify state-of-the-art analytical methods as determined by scientifically objective criteria (for example, sensitivity, specificity and limits of detection) and lead the establishment of standards across Federal, state and local governments and authorities for the testing for pathogens in water, the environment, food supplies to protect human health. We suggest that agreement by stakeholders upon the validity of specific analytical methods for pathogen testing and establishment of standards implementing such methods will result in the creation of a market that will be attractive for the commercialization of biotechnology tools and platforms for testing water. We further suggest that a standards-making authority such as the Stakeholders' Panel on Agent Detection Assays (*SPADA*) and AOAC

International as a standards implementation organization be formed to accomplish this step.

2. Invest in the development of new applications based on proven testing methodologies that have demonstrated an impact in existing applications of biotechnology tools and platforms. For example, human clinical diagnostics have proven the effectiveness of genomics in improving health outcomes for humans. That same genomic technology can be applied to protect food supplies, water supplies and the environment. http://www.cev.washington.edu/story/Ecogenomic+Sensor

3. Make protection of our water resources a federal funding priority: Genomic sensors placed within the infrastructure that is part of the Ocean Observatories Initiative (OOI) should be prioritized to provide high-resolution information on the biology of our oceans and extend the program to include testing and analysis of our freshwater resources.

4. *In order to move life sciences breakthroughs from lab to market* (by overcoming the risk, expense, and need for many years of sustained investment), we suggest that the federal government continue to support regional, state and local small business incubation efforts. We also believe the federal government should improve access to federally funded inventions by being more flexible in granting licenses to those inventions.

Thank you very much for providing Spyglass and FAS LLC an opportunity to respond to OSTP's RFI. We hope that our input is helpful in developing the National Bioeconomy Blueprint.

Chris Melançon
Spyglass Biosecurity, Inc.

Daniel Mazella, J.D.
Farragut Advisory Services LLC

Building a 21st Century Bioeconomy

Fostering Economic and Physical Security Through Public-Private Partnerships and a National Network of Community Labs

Rob Carlson, PhD

What is the Bioeconomy, How Big is it, and How Fast is it growing?

Biological production is a substantial economic and employment opportunity for the United States. While the U.S. economy already depends heavily on biology, primarily via production in the agricultural sector, new technologies will enable the biomanufacturing of large volumes of fuels, materials, and enzymes. I hereafter refer to the totality of biological production in the U.S. economy as the "bioeconomy".

According to the USDA Economic Research Service, the U.S. agricultural sector added $331 billion to the economy in 2009[1]. This figures is impressive, but revenues from biological technologies are rising rapidly and will soon surpass those from agriculture alone.

A recent estimate published by Biodesic put total U.S. revenues from genetically modified (GM) products at more than $300 billion annually[2]. While "biotechnology" is typically thought of as either drugs or crops, a more detailed look at the sector reveals instructive complexity. Biologics (biotech drugs) had sales of approximately $75 billion in the United States in 2010. GM crops brought in at least $100 billion in farm scale revenues and GM seeds added another $10 billion. Industrial biotechnology, including biofuels, industrial enzymes, bioplastics, and other materials, generated sales of $115 billion[3]. Revenues from GM crops and biologics are growing at approximately 10% annually, while revenues from industrial biotechnology are growing at 15–20% annually.

1 See "Table 29—Value Added to the U.S. Economy by the Agricultural Sector" http://www.ers.usda.gov/Publications/AgOutlook/AOTables/CurrentTables/aotab29.xls

2 Carlson, R., "Biodesic 2011 Bioeconomy Update", Aug 2011, DocID: 20110811_01 http://www.biodesic.com/library/Biodesic_2011_Bioeconomy_Update.pdf

3 For a discussion of the methodology used to derive these figures, and of the resulting uncertainties, please see Carlson (2011).

2010 U.S. revenues from genetically modified products were greater than $300 billion, or the equivalent of more than 2% of GDP.

The difference in growth rates is partly explained by the high cost of developing new biologics and new GM crops. The high costs, in turn, are partially explained by the regulatory barriers accompanying drugs, food, and the environmental release of novel organisms. In contrast, most industrial applications are unregulated because they are used for materials production and do not involve the environmental release of GM organisms. In other words, the largest and fastest-growing subsector of the bioeconomy is generally not subject to regulation.

The United States is on course to dramatically increase its reliance upon biological technologies for the production of food, drugs, materials, and fuels. The relative contribution of the different sectors to the total is worth considering. In the past, drugs dominated "biotech" revenues in the United States, but today this contribution accounts for less than half the total. As biological technologies mature, becoming more useful and prevalent across different sectors of the economy, industrial and agricultural applications will amount to an ever larger share of total revenues. But, in order to foster the necessary *amount* of innovation to supply new technologies domestically, we must foster the necessary *structure* for that innovation.

The U.S. Economy Begins in Garages

Start-ups and small organizations are at the heart of both innovation and job creation in the United States. A recent re-analysis of Census Bureau data published by the Kauffman Foundation determined that 100% of net job creation in the United States is due to start-up companies[4]. Companies in their

4 Kane, T., "The Importance of Startups in Job Creation and

Table 1: Important Innovations By Small U.S. Firms, 1900–2000

Air Conditioning	Geodesic Dome	Polaroid Camera
Air Passenger Service	Gyrocompass	Portable Computer
Airplane	Heart Valve	Prestressed Concrete
Articulated Tractor Chassis	Heat Sensor	Prefabricated Housing
Assembly Line	Helicopter	Pressure Sensitive Tape
Audio Tape Recorder	High Resolution CAT Scanner	Programmable Computer
Bakelite	High Resolution Digital X-Ray	Quick-Frozen Food
Biomagnetic Imaging	Human Growth Hormone	Reading Machine
Biosynthetic Insulin	Hydraulic Brake	Rotary Oil Drilling Bit
Catalytic Petroleum Cracking	Integrated Circuit	Safety Razor
Cellophane	Kidney Stone Laser	Six-Axis Robot Arm
Artificial Skin	Large Computer	Soft Contact Lens
Computerized Blood Pressure Controller	Link Trainer	Solid Fuel Rocket Engine
Continuous Casting	Microprocessor	Stereoscopic Map Scanner
Cotton Picker	Microscope	Strain Gauge
Defibrillator	NMR Scanner	Strobe Lights
DNA Fingerprinting	Optical Scanner	Supercomputer
Double-Knit Fabric	Oral Contraceptives	Two-Armed Mobile Robot
Electronic Spreadsheet	Outboard Engine	Vacuum Tube
Freewing Aircraft	Overnight National Delivery	Variable Output Transformer
FM Radio	Pacemaker	Vascular Lesion Laser
Front-End Loader	Personal Computer	Xerography
	Photo Typesetting	X-Ray
		X-Ray Telescope
		Zipper

Source: U.S. Small Business Administration

first year of business create an average of 5.7 jobs, for a total of 3 million new jobs per year nationwide, while "all other ages of firms are net job destroyers."[5]

Small firms are also responsible for an impressive array of innovations now driving the U.S. economy. Table 1 includes a list—literally A to Z—of important innovations provided by small firms during the 20th century[6]. Mature products based on these technologies are unlikely to be mass-produced in garages, but garage innovation played a critical role during their development.

Recommendation 1: An innovation and job creation blueprint for the bioeconomy must include fostering large numbers of start-up companies.

Many of the technologies listed in Table 1 passed through garages as part of, or as a result of, dramatic reductions in cost. Those cost reductions further increased access, which consequently led to innovation that further reduced cost. Biotechnology has been experiencing exponential decreases in cost for several decades[7]. Prices fell precipitously during this period, though they remained sufficiently high to limit access to well-funded academics and relatively large or well-funded companies. Within just the last few years, costs in biotechnology have fallen to the point where a credit card with a modest spending limit is sufficient to outfit a capable laboratory with used equipment. As a result, garages are now beginning to shelter hobbyists, artists, and entrepreneurs interesting in building a new world using biology[8]. Given the history of U.S. innovation, we should expect that burgeoning garage innovation in biology (not just biotechnology) will provide seeds for a more pervasive and more valuable bioeconomy.

Job Destruction", July 2010, The Ewing Marion Kauffman Foundation.

5 ibid.

6 This particular list is from Baumol, W., "Small Firms: Why Market-Driven Innovation Can't Get Along without Them", U.S. Small Business Administration, 2005, p 183, from the original in U.S. Small Business Administration, Office of Advocacy, "The State of Small Business: A Report to the President", Government Printing Office, 1994.

7 Carlson, R., "The Pace and Proliferation of Biological Technologies", *Biosecur Bioterror,* 2003;1(3):203-14; Carlson, R., *Biology is Technology*, Harvard University Press, Cambridge, MA 2010.

8 Ledford, H., "Garage biotech: Life hackers", *Nature* 467, 650-652 (2010).

Fostering Safe and Secure Garage Innovation in the Bioeconomy

Any honest appraisal of the broad proliferation of a powerful technology must acknowledge both opportunity and risk. As described above, there is a large economic opportunity in embracing innovation in biological technologies and historically this innovation has often been found in garages. Given that biological technologies might be used in ways that cause accidental or intentional harm, how might we encourage garage innovators in biotechnology to conform to practices that reduce risk?

Community labs now emerging across the country are an excellent opportunity for the U.S. government to engage budding biological innovators on multiple fronts. The National Bioeconomy Blueprint should include support for a greatly expanded network of community labs through public-private partnerships. The purpose of the network is multifold: 1) the network will provide infrastructure to support "garage style" start-up activity; 2) community labs will enable participants to share information and resources to accelerate their own progress; and 3) community labs will facilitate the ability of the U.S. government to engage the community in discussions that range from Grand Challenges to biosecurity.

Recommendation 2: The National Bioeconomy Blueprint should include support for a network of community laboratories that would provide access to infrastructure, increase communication between innovators, and facilitate engagement with the U.S. government in regards to national security and national technology development goals.

It is already feasible to build a functional garage lab for as little as $500, assuming one has access to a garage or similar space[9]. However, R&D efforts aimed at commercialization are likely to require greater resources and will usually benefit from dedicated space. It is also generally far easier to work in a biology lab populated by people who may know tricks of the trade or be able to spot potential mistakes. Therefore, access to a larger community laboratory space could enable more innovation and communication among entrepreneurs building the bioeconomy.

A network of community labs would also provide an opportunity to improve security and reduce risk. Because biotechnology is already so widespread, it is likely that reducing risk will be more readily accomplished through building open networks that increase information transfer than by attempting to prohibit or control access to the technology[10]. Indeed, The National Strategy for Countering Biological Threats has identified broad access to biological technologies as a key component of physical and economic security; "The beneficial nature of life science research is reflected in the widespread manner in which it occurs. From cutting-edge academic institutes, to industrial research centers, to private laboratories in basements and garages, progress is increasingly driven by innovation and open access to the insights and materials needed to advance individual initiatives."[11] The National Strategy explicitly recognizes that as costs continue to fall, and as skill and access proliferate, we should expect important innovations to be generated in "basements and garages". Going beyond this recognition, the National Bioeconomy Blueprint should include strategies that actively engage innovators in a conversation around 1) the risks and benefits of biological technologies and 2) priorities for technology development in the service of national needs ranging from environmental monitoring of pathogens, to new human and animal diagnostics, to biofuel production technologies.

The FBI already has a program in place to facilitate communication between its agents, local law enforcement, and biotechnology innovators working in unconventional settings[12]. As a result of this process, innovators and artists are reassured that the FBI's primary interest is public safety and security, and the law enforcement community is introduced to the mindset and working environment common in garages and community labs. This ongoing conversation should serve as a foundation for extending the model of engagement beyond national security and law enforcement policy to become a pillar of national economic policy.

Supporting the Formation and Funding of Community Labs as a National Resource

Existing community labs have been set up in empty office spaces and mixed-use buildings

9 Brunstein, J., "The quest for the $500 home molecular biology laboratory", http://www.mlo-online.com/features/201112/tips-from-the-clinical-experts/the-quest-for-the-500-dollar-home-molecular-biology-laboratory.aspx

10 See Carlson (2003) and Carlson (2010).

11 "National Strategy for Countering Biological Threats", National Security Council, November 2009, http://www.whitehouse.gov/sites/default/files/National_Strategy_for_Countering_BioThreats.pdf

12 See Ledford (2008).

around the country. These facilities are supported by a combination of donations, membership fees, and revenues from courses that cover everything from ecology, to genetic engineering, to growing functional architectural elements out of mushrooms.

The funding requirements for these facilities are generally modest. They are typically set up as non-profit organizations, and are therefore eligible to receive grant support and donations of equipment. The National Bioeconomy Blueprint should forward guidelines that clearly identify the roles and responsibilities of community labs—and of members of those labs—that would enable qualifying labs to receive government grants of financial support, surplus equipment, and expired but still useful laboratory supplies.

Recommendation 3: The National Bioeconomy Blueprint should contain guidelines that clearly identify the roles and responsibilities of community labs—and of members of those labs—that would enable qualifying labs to receive government grants of financial support, surplus equipment, and laboratory supplies.

An alternative approach to the direct funding of non-profit community labs might be grants to local governments to fulfill the same role. Local libraries are already examining ways to expand their offerings beyond books and internet access to hosting "Maker spaces" with 3D printers and computer controlled machine tools[13]. These efforts could be expanded to add or convert space in public libraries into community labs that promote the safe and secure learning and practice of skills related to biological technologies. This strategy would build upon the long relationship the public has with libraries as a resource at a time when many of those facilities are seeing less use due to electronic books.

In general, the National Bioeconomy Blueprint should make it easier for innovators to try ideas. Facilities within the community lab network would not need to be elaborate, perhaps only providing access to basic laboratory needs such as a sink, deionized water, freezers, and waste disposal, while leaving other expenditures to "members". Publicly funded community labs could still charge for classes or sublet space to start-ups. One component of a successful application for government support of funds or material might be a financial plan that leads to self-sufficiency. These facilities should not be viewed as "incubators" per se, or at least not as envisioned by venture capital firms and many state agencies. Community labs, as described here, should probably not aim to generate revenue. Policy makers should recognize that some subsidy may be acceptable in exchange for the public good of a safer network and greater overall innovation.

Conclusion

If the past is any guide, producing future biotech innovation will require the involvement of small businesses and entrepreneurs. Government policies intended to foster economic growth and job creation are therefore best focused on facilitating the founding of start-ups and their participation in domestic and global markets. One mechanism of connecting small business with consumers would be the continued expansion of the USDA Biopreferred Program to include a greater array of products, and to include certification of products that are the subject of large daily demand on "Main Street".

The National Bioeconomy Blueprint must include the contributions of small organizations. Defining standards and a national role for community labs, and then supporting those labs, will improve both economic and physical security.

More information is available at www.biodesic.com

13 Reeder, J., "Are Maker Spaces the Future of Public Libraries?", http://www.shareable.net/blog/the-future-of-public-libraries-maker-spaces, and Torronne, P., "Is It Time to Retool Public Libraries as TechShops?" *Make*, 28, 28, and http://blog.makezine.com/archive/2011/03/is-it-time-to-rebuild-retool-public-libraries-and-make-techshops.html

Microbrewing the Bioeconomy:

Innovation and Changing Scale in Industrial Production

Rob Carlson, Rik Wehbring

The future of the U.S. economy might be found in a pint of beer. The rise of craft brewing in the United States is a fascinating test case of distributed biological manufacturing emerging in a market dominated by large scale industrial production. Microbreweries today compete successfully in a commodity market with the largest of multinationals, suggesting that small scale biological manufacturing may be even more successful in higher margin markets. Over the coming decades advances in biotechnology will improve the feasibility and competitiveness of manufacturing firms of all sizes.

How Big is the Bioeconomy?

Biotechnology is often associated with just two markets: medicine and agriculture. Yet the role of biology in the economy is pervasive and there are many more markets and many more dollars at stake. For example, the biofuels industry is concerned not just with liquid fuels and agricultural feedstocks, but also with producing enzymes, metabolic pathways, and organisms that convert biomass to fuels. More broadly, industrial biotech uses biology to replace industrial processes in the manufacturing of the products of everyday life. Revenues from industrial biotech in the U.S. are already larger than medicinal or agricultural biotech and are growing roughly twice as fast. In 2010, total U.S. revenues from genetically modified (GM) drugs were roughly $75 billion, total revenues from the three largest GM crops were approximately $80 billion, while revenues from GM industrial biotechnology were about $100 billion.[1]

A low regulatory burden clearly contributes to the high growth rate of industrial biotechnology. Whereas new drugs or crops require years of testing, which increases both cost and time to market, new bioplastics, biofuels, or industrial enzymes face little or no regulatory barriers to the marketplace. The critical role of regulation can also be seen in the history of the brewing industry in the U.S. Understanding the interrelated roles of technology, regulation, and demand in brewing serves as an excellent starting point for thinking about the future of the bioeconomy.

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Fermentation is an example of a widely distributed biological technology used to produce everything from laundry enzymes, to vitamins, to beer. The evolution of brewing economics and technology in the United States provides an example of meeting market needs via distributed biological manufacturing.

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After Prohibition, regulatory structures kept small businesses out of the brewing market. With the aid of refrigeration and transportation, large scale breweries proliferated. Subsequently, industry consolidation set in and the number of breweries in the United States shrank. In 1979, the passage of the Cranston Act allowed individuals to brew 100 gallons a

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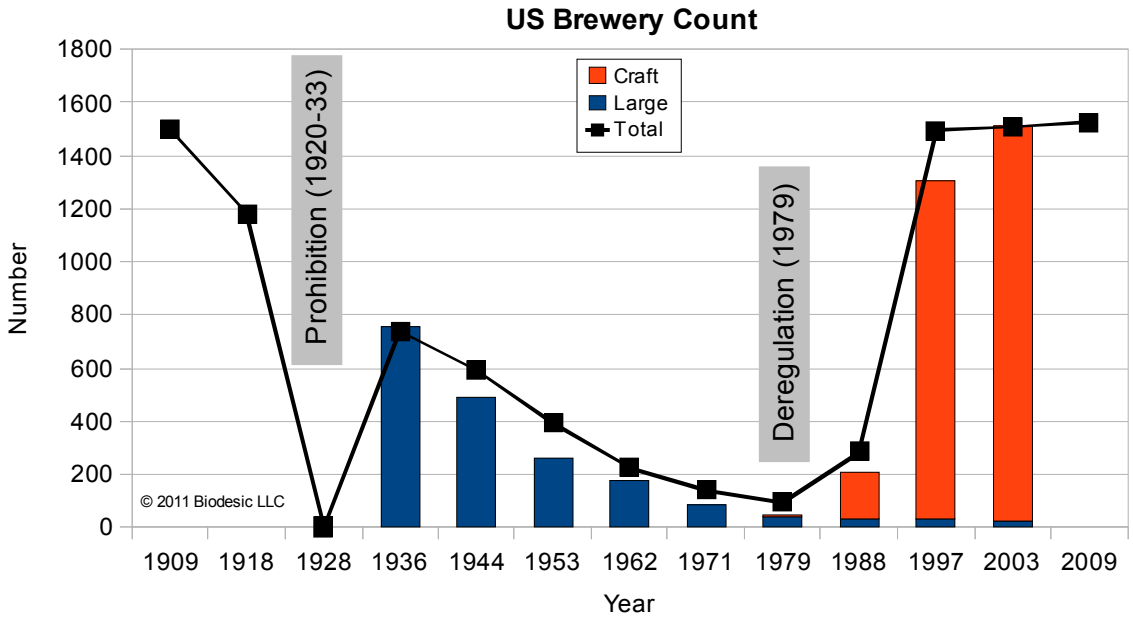

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The growth in the United States of a new industrial sector shows that small scale, distributed production can compete against an installed large scale infrastructure base. According to the Brewers Association, as of the middle of 2009 there are about 1,500 craft brewers in the United States, about 20 large brewers, and about 20 "others", with brewpubs accounting for about 2/3 of the craft brewers (Figure 1).

Conclusion 1: Emerging small scale, distributed production can compete against an installed large scale infrastructure base.

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Conclusion 2: Small scale producers can command a premium in a commodity marketplace.

Labor & Innovation

Growing markets and high profit margins are important demand-side considerations. However, businesses are also concerned with supply-side considerations such as the availability of skilled labor and a steady flow of innovation to avoid commoditization. Home brewing had been rare in the United States prior to 1979, which points to an important feature of the market; namely, that the skill base for brewing was quite limited. Yet another effect of legalizing home brewing was that people could practice and build up their skills; they could develop new recipes and explore new business models.

The craft brewing movement developed a culture of innovation which extends to technology development. Homebrewers are now incorporating advances from the open source hardware and software communities into their projects. For example, the Brewtroller Project is an "open source community focused on developing and supporting control systems for brewing beer".[6] The hardware is based on the open source Arduino microcontroller and the associated community makes available schematics, parts lists, process code, and recipes. Notably, the goal of the software portion of the project is a program that "will walk through a series of stages (some optional) such as filling, preheat, dough-in, protein rest, acid rest, saccharifaction rest, mash out, sparge, boil and chill."[7] This is a complicated process that is presently directed toward producing the perfect pint. However, the instrument is complex enough to grow a wider variety of organisms than just yeast and to produce a wider variety of substances. The Brewtroller also reduces the skill level required to use fermentation enabling a greater number of individuals to brew beer, produce recombinant proteins, or in other ways join the bioeconomy.

Historical Lessons

In summary, the proliferation of distributed biological manufacturing that followed the legalization of craft brewing in the United States provides three general lessons relevant to considering investment in the future bioeconomy. First, it is clear that, given access to tools and skills, entrepreneurs can innovate and change markets even when those markets are dominated by large companies. Craft brewing emerged in the United States amidst an already established large scale, industrial infrastructure for producing and distributing beer. Second, small scale, distributed production can command a premium at the cash register. Third, the largest shift in the transformation of the U.S. brewing industry came about 10 years after deregulation (See Figure 1). Revolutionary change may have a long lead time, but the ensuing market transition can be quite sudden.

Structural Changes in the Marketplace

It is often said that greater efficiency is found in greater scale or, in other words, that economies of scale always favor large production facilities. This is true for many industrial activities, for example all throughout the petroleum industry, in which both thermodynamics and surface-to-volume considerations favor larger ships, larger storage tanks, and larger refineries. Consider also steel making, where one large blast furnace is more efficient than a hundred smaller smelters. This is an assertion that China unwittingly tested during the Great Leap Forward of the 1950's when peasants were directed to create backyard smelters and promptly cut down 10% of China's trees for fuel in just a few months, while producing only piles of useless low quality ore that still

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Those participants will have access to an increasingly mature marketplace. Even a decade ago, to attempt a genetic experiment required a monolithic, vertically integrated, strategy. Producing a product based on a genetically modified organism required in-house expertise in a wide range of skills spanning biochemistry, molecular biology, and microbiology. Yet within the last few years every one of these specialized skills has become available for purchase as a service in a competitive marketplace. Specialization creates new niches where companies can thrive; it also facilitates proliferation and competition. It is now quite simple to find an interesting gene sequence in an online database, electronically submit this to a DNA foundry to be fabricated, and have the resulting molecule shipped to a protein expression house for manufacture and delivery to your doorstep. This protein could be used as a tool in house or could be immediately reshipped as a product. That the skill base for genetic modification has recently seen a rapid proliferation suggests we may soon see an economic disruption analogous to the transformation of the brewing industry. However, given the great breadth of application of genetic modification, the resulting disruption could lead to far greater change within our economy

Conclusion

The bioeconomy is much bigger than recombinant insulin or genetically modified corn. Increasingly, ordinary industries outside medicine or agriculture will be transformed through the adoption of biological technologies. Technological change always brings the possibility economic disruption and produces new winners or losers. One significant aspect of biotechnology is that the economies of scale are very different from those of previous technology revolutions, such as chemistry, and may favor smaller, distributed production rather than enormous centralized facilities. The historical example of microbrewing demonstrates that these ideas are not just theoretical, but very real. Intense small scale innovation, coupled with biotechnology, has allowed microbrewers to gain a share of the beer market and be more profitable than traditional macrobrewers. The transition to a bioeconomy is just beginning and the years of disruptive change are still ahead.

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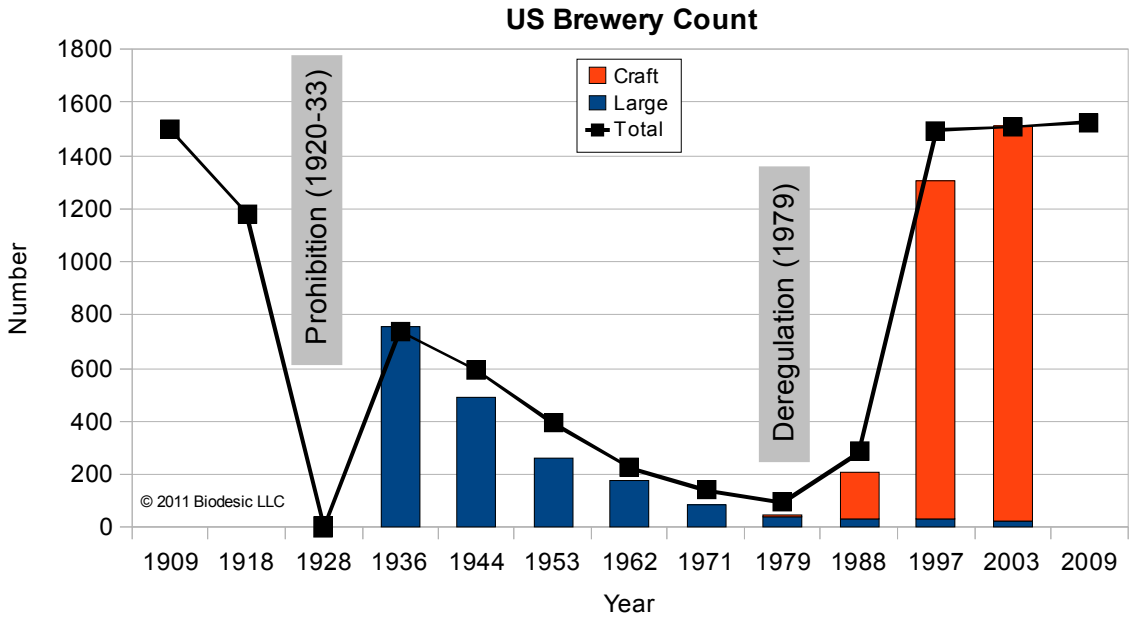

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Submitted in Response to RFI: Building A 21st Century Bioeconomy (OSTP)
Jonathan Kuniholm (Capt (Ret) USMC-R), President, Open Prosthetics Project
[redacted]

Grand Challenge: Deliver A Bionic Arm for Veteran Amputees
Bionic arms are not yet here. We've spent hundreds of millions of dollars on prosthetic arm research since the spike of arm amputation injuries in our wars, but *not one single new prosthetic arm device or component has been introduced to market as a result.* It's time to keep the promises that we have made to our veterans.

We need grand challenge to deliver a real bionic arm. Because this can't happen in a single step, the challenge will consist of an annual list of tasks on which entries will be evaluated, and we will continue the challenge until we have succeeded. All tasks must be performed under amputee control, the arms worn by real amputees of various levels, and the arms completely self-contained. The final challenge will be a competition against a human arm.

The challenge will be modeled after the DARPA Grand Challenges with important exceptions. Using the values of "cooperatition" and "gracious professionalism" championed by the FIRST Robotics League, the challenge will be based on and will encourage the shared development of the electromechanical and software tools necessary to participate in the challenge, and collaboration among the participants will be encouraged (but not required) through the structure of the challenge, and through the use of this shared platform.

Policy Recommendations for "Orphan Device" Innovation

- **Common platform and "app store" for encouraging collaboration**
- **Private corporation "The Stumpworx," owned by disabled vets to commercialize and shape priorities**
- **SDVOSB set-asides for consumer businesses that serve owner interest**
- **Coordination or at least transparency in single-topic government funding**
- **SBIR/STTR programs designed to work with overall strategy**
- **Voluntary industry standards for interoperability and interconnection with support to non-profits to maintain them**
- **FDA policy that encourages development of new orphan devices**
- **Eliminate the FDA's "Class III Cootie" problem with modular systems**
- **CMS (Medicare) reimbursement as an incentive for innovation**
- **Exercise government license or Bayh-Dole "march-in" in failure to perform**
- **Funding for student projects and programs at all technical levels that serve orphan device communities and encourage contribution to the commons (workforce)**
- **Use "Vehicle Forge" collaboration platform for development**
- **Better information about funding opportunities that allows outside web 2.0 markup and organization**

An Arm Development Platform to Build From—An App Store for an Android-like Ecosystem
Recent investigations into replacing arms with bionics and prosthetics show promise, but the challenge is huge, and we've only begun. In order to leverage the technology we've already developed, we need a common platform for further electromechanical and software development. This will help lower the marginal cost of innovation, and increase its pace. By taking the greatest advantage of research to date, we can ensure going forward that research initiated by the government builds on what has already been achieved, rather than duplicating it, or falling short. Anyone who wants to go it alone is welcome.

Initially, we hope to support the creation of the platform through a voluntary research consortium consisting of a **public-private partnership** of technology stakeholders from the DARPA Revolutionizing Prosthetics Project, non-profit and consumer advocacy groups, private

companies, government-funded academics, and their funding agencies. Through the structure of the research platform hardware and software, which will be created in the mold of the Android smartphone ecosystem, participants can develop incremental or revolutionary improvements at any level that they choose. The use of common software and hardware protocols will allow the creation of hardware peripherals and software "apps" that allow the participants to mix and match the best of their efforts to solve common goals. As smartphone ecosystems have encouraged rapid and explosive innovation, so too I hope that this platform can not only make the most of existing and future government research expenditure, but also make it easier for private investment to have an impact in this underserved area.

The creation of this common research and development platform will serve as a model for innovation not just in prosthetics and robotics, but also in the service of other disabilities similarly underserved by our health system— what can be called "Orphan Devices." This common platform will center the larger public-private partnership that must be created to bridge the so-called "valley of death" that separates research from real products. By bridging the divides of communication and collaboration among the players—government, academia and industry—who have failed to solve these problems on their own, we can also bridge the valley of death that has separated them from results.

DARPA's "Vehicle Forge" platform currently under development could be a model for integrating innovation from a combination of government and private sources.

Crossing the Valley of Death—Getting *Orphan Devices* to Market
While this is a commonly acknowledged problem, it is not one that anyone has convincingly addressed. As discussed above, government research hasn't produced any new devices that patients have access to. This is a source of embarrassment and frustration for all of us who have worked hard on these programs, as well as for all of us who are waiting for a solution as patients.

The problem is, in general, not a technical one or a regulatory one, but an economic one. There are simply not enough arm amputees in America or the rest of the world with the health care resources to warrant private investment in solving the problem. In parallel with orphan drug populations numbering fewer than 250,000 patients, the 41,000 arm amputees in America require an even more challenging remedy—the orphan device.

No venture funding is going to target a market in which investment is unlikely to be recovered at all, much less yield a seven-fold or larger return. The problem consists of a multiple market failure that has been solved neither through government funding and academic research, nor by the private sector. Any potential solution must involve the better coordination of each of these sectors, through creative approaches, to take advantage of the strengths of each one.

This is a challenge that we must overcome as a society, and it is by no means unique to prosthetic arms. Of the more than 6,000 orphan conditions listed by NIH, missing an arm is not one of them. This document mentions multiple strategies, based on responses to the RFI, which might be used to successfully attack this problem.

Stumpworkx: A Service-Disabled Veteran Owned Small Business as Part of the Solution
No one is more personally invested in finding a solution to the problem of missing an arm (or any medical condition) than someone who suffers from the problem. I have begun the development of a venture owned not just by a single veteran arm amputee, but by ALL of them. By early 2012, Stumpworx will be incorporated. This venture will be part owned, according to its bylaws, by every service-connected arm amputee rated for disability by the DoD or the VA for the amputation of at least a hand. Through what I call a private-sector entitlement, veterans who have lost their arms in the service of their country will have a seat at the table in deciding what products we as a company develop on our own behalf. Shareholder meetings will likely end up being some of the best market research the industry has ever seen.

This company has been conceived based on the premise that it is possible to best serve patients in this orphan device market not by protecting good ideas as intellectual property, but by sharing our ideas and inviting others to help us solve this difficult problem. I am starting this business because the private sector has not stepped in to commercialize any of the next-generation technology developed by the government for prosthetic arms over the last decade. Most tragically, and in stark contrast to what happened after World War II, neither industry nor government has stepped in to improve any of the previous generations of technology. I wear a hook that still bears the name of the man who patented it in 1912, despite two corporate acquisitions since 1960. Though I have shared several ideas for more incrementally improved prosthetic components, such as a body-powered harness, these things have gone unnoticed and unexploited by the prosthetic industry. This venture is an acknowledgement that sometimes, you have to do things yourself if you want them done (the lesser-known seventh troop-leading step, BAMCIS-**D**).

I hope that Stumpworx will be able to work closely with the government agencies that fund prosthetic research, and the recipients of funding, to improve both the quality and focus of this funding, as well as the sector's track record for successful commercialization.

The Open Prosthetics Project—More User Feedback and Involvement
A 501(c)3 non-profit, the Open Prosthetics Project is an online community consisting of a collection of low-cost websites dedicated to the sharing of ideas about prosthetic design, and as a patient community for discussing all of the issues surrounding our common physical challenges. The project includes a number of initiatives that will be expanded and supported by Stumpworx, in much the same way that Google, IBM, Red Hat and Buglabs work with the open source communities they support and benefit from.

The Open Prosthetics Project (OPP) appears in the first page of Google results for "prosthetics," which I think says more about the poor quality of information available to amputees online than it does about the quality of what we provide. That said, I think that we have accomplished quite a bit without any resources, and compare favorably with The National Resource Directory (http://nationalresourcedirectory.gov/), Disability.gov, www.prosthetics.va.gov, or any number of much better funded websites.

We have a number of ideas for the expansion of the features offered by the website, and it is our hope to interest others in the shared development of these features and the expansion of similar sites serving many communities of this kind. One such idea could be government-funded tools that would help websites like mine interface with government funding data and other resources.

Industry Standards for Interoperability
OPP has been proposed as a shepherd organization for a couple of open standards that are being developed in the prosthetic industry, a mechanical wrist connection standard and an electrical communication bus standard (see attached letters of support from industry for this standards initiative).

Regulatory Barriers
FDA regulation of prosthetic arms is absolutely NOT a barrier to the introduction of new prosthetic arm components as they exist and as the FDA currently interprets these regulations. Over the past few years, multiple new articulated hand devices have been introduced as Class I (Exempt) devices, exempt from both 510(k) Premarket AS WELL as the most basic Good Manufacturing Practices (GMP) and Quality Controls (QC) required of other Class I devices. This includes the most advanced myoelectric hands, hooks, wrists and elbows.

Unfortunately, the FDA has threatened to regulate similar devices as other than Class I (Exempt). Indeed, both DARPA Revolutionizing Prosthetics programs (2007 and 2009) have made inquiries to the FDA about the possible future classification of their devices. The answers have not been made public, and the message on this topic from the FDA has been both inconsistent and

confusing. I have called multiple officials at FDA, and have been unable to get a straight answer about the way that articulated electromechanical hands and arms are to be regulated in the future. This is at least in part due to FDA's historical role serving companies and regulating individual products, with absolutely no transparency regarding applications and records. Even as multiple highly articulated hands are introduced into the US as Class I (Exempt) devices, *the threat of more stringent FDA regulation* looms as a specter discouraging action and investment by others. Note that nearly identical devices are sometimes classified differently—Otto Bock Myo Boy (Class I Exempt) and Motion Control Myolab (Class II)—and even the manufacturers cannot tell you why this might be. I asked both, and both said it made no sense.

The FDA's Innovation Pathway
The DARPA Revolutionizing Prosthetics 2009 (RP 2009) Arm, developed by Johns Hopkins Applied Physics Lab and collaborators, was recently chosen as the FDA's model system for an accelerated approval process. While failing to acknowledge FDA's current treatment of similar Class I (Exempt) devices (similar excepting the neural interface, which is far from ready for human amputee use), the FDA has pressed forward and appears poised to classify all of the modular electromechanical components of the arm as part of an invasive Class III system, and the similar electromechanical components of the RP2007 arm as Class II. While the FDA may not currently be the real barrier to the introduction of these devices to market, this "streamlining" initiative, in addition to their responses on related devices, has the potential to *become* the reason.

An Alternative Pathway—Orphan Device Regulation as an Incentive to Innovate
Despite the fact that no commercial partner has been identified for the RP 2009 Arm, the entire system was announced as the model device for the Innovation Pathway. At the public announcement of this initiative, there was a lot of public griping by major medical device companies because their pet devices were not to be included in this initial program to fast track approval. I suggest that this is an opportunity for the FDA to take leadership, and rather than trying to use the prosthetic arm as a model for fast-tracking a device that assumes a commercial impetus to do it (with no commercial partner in sight anyway), instead creating a program that *incents development in orphan devices*. In contrast to dealing with complaints of "why wasn't my cardiac device fast tracked," the FDA could instead field requests to help with the development or production of the prosthetic arm or other orphan device.

FDA could in fact work in conjunction with the Centers for Medicare & Medicaid Services (CMS) to try and incent innovation with the promise to reimburse for certain capabilities or achievements, paying only for clinical results, without necessarily having to fund the development (see below for further discussion).

An important note on orphan devices: The orphan drug law creates incentives for pharma to produce these drugs by extending exclusivity. In prosthetic arms, the existing exclusivity available to patent holders is not being taken advantage of. Prosthetic arm patents, because of the small patient population, are routinely abandoned and maintenance is left unpaid after 7 or 15 years. At least for arm devices, extending exclusivity is not a viable solution.

Focusing Priorities in Research and Technology Development
The traditional model for moving technology from the lab to the market is for the university or professor involved in the research to license the technology for a fee to someone who seeks to spend additional funds (sometimes 90 per cent of the total R&D cost) to bring a product to market. For orphan devices there is no such incentive. Further, the university and professor share the desire to continue to perform funded academic research, rather than be involved in the details of commercialization. Government lab work is no different when focused on underserved areas—the lab's interest is usually driven by the research rather than the commercial interest. The focus on neural devices in prosthetic research, for example, ignores myoelectric pattern recognition technology, which was pioneered in the lab decades ago, and the few patents were abandoned or have expired. Commercial devices were never developed.

Government Funding for Prosthetic Arms Not Coordinated and Not Transparent
There are at least eight government agencies that have funded prosthetic arm research. These programs are often duplicative, almost never coordinated, and specific performers tend to be favorites of certain funders. Announcements of funding are generally available by source and not by topic, so even the portfolio managers at given agencies are unaware except by personal connection of what their counterparts are up to. Research.gov and grants.gov offer a limited picture and have bad search tools. Making the data available in a common platform across agencies so that outside groups (Google, or Open Prosthetics, *e.g.*) could organize the content in meaningful ways (socially) would be a much better alternative. See initiatives like Mendeley, Zotero, etc.

A new model that encourages researchers to use technology for research that can simultaneously be developed into medical device products by a company devoted to serving both labs and patients is a potential answer. By initially serving labs, and providing them with devices more capable and reliable than their students or researchers can produce on a prototype basis, such a company can transform these devices from prototypes around which many engineers must hover to keep running, to products that are capable and reliable enough to be commercially produced. Evidence of their use in clinical settings could certainly support this goal.

Knowledge in the Service of Society
While academic institutions seek to increase knowledge for its own sake, they also seek to place that knowledge in the service of society. To the extent that the government, in seeking input on this initiative, shares the same goal, it seems reasonable to tailor funding mechanisms to encourage or even require the commercial use of the results.

The Bayh-Dole Act "march-in" provisions actually allow the government to reassign IP generated by its funding if, at the agency level, it is determined that the "action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use" (35 U.S.C. § 203). While this has never been exercised, it's hard to imagine a more acceptable situation than when government-funded intellectual property designated to help those suffering from a rare medical condition has failed to deliver on the promise.

Grand Challenge Through Centers for Medicare & Medicaid Services (CMS)
Current reimbursement for prosthetic devices is governed by the "L-codes" for durable medical equipment set by CMS. Interestingly enough, although there is no reason other than convenience for it to do so, government procurement of these devices provided for veterans and active duty military through contractors (the majority of arms) are likewise priced according to these L-codes.

The procedure for creating new CMS L-codes and setting reimbursement levels for them is far from transparent. The list of codes reads like a partial catalog of devices: "Otto Bock Speed Hand, or Equivalent," for example. Because of this, the codes encourage a "race to the bottom," and many competitors products are simply cheaper devices that provide the same limited functionality, increasing providers' profit margins and offering patients nothing more than the original products.

Imagine if CMS were to offer the guarantee of reimbursement for a set number of patients through Medicare for a device that met certain performance criteria. Then, for a known outlay of government funds, the government could guarantee that the funds would only be spent if the devices reached market. While this doesn't guarantee that it would happen, it does guarantee that the money would not be spent unless it did. This strategy could certainly be part of, or even represent the culminating test of an annual competition and ongoing grand challenge.

Targeting STTR/SBIR Funding
To the extent that some government-funded intellectual property has gone unexploited by the

recipients of funding, STTR and SBIR funding mechanisms are a great way to encourage commercial development. That said, quite a number of prosthetic projects have gone through Phase II never to reach Phase III, where commercial funding is required. Bayh-Dole march in in these cases is a viable option as well, and perhaps even more justified, given the commercial focus of these mechanisms.

Alternatively, STTR/SBIR funding could be targeted at further developing open platforms such as that described in this document. Such funding could be dedicated toward creating commercial products based on such platforms, or on technology developed under other funding sources that has never been commercialized.

SVDOSB Set Asides
The government routinely favors Service Disabled Veteran Owned Small Business in contracting, and it stands to reason that such preferences could be extended to companies applying for research grants or contracts to help develop assistive technology, particularly when those vets represent the community that the funding is intended to serve.

From personal experience, I can relate an instance in which a reviewer heavily criticized a prosthetic arm-related SBIR proposal from a business perspective because the prosthetic arm market was so small. Obviously, if such funding mechanisms are to be targeted at underserved patient populations, any such concerns must be waived in advance, or STTR/SBIR mechanisms should be created specifically to target these markets.

Workforce development
I spend a lot of time telling students that prosthetic arms are not as advanced as they think that they are, and that they are unlikely ever to find a job as a prosthetic engineer, because there are so few of them. That has done little to dampen most of their enthusiasm, and it's an enthusiasm that we should channel. In general, students are extremely motivated to work on social problems, and we should figure out a way to try and put them productively to work.

If we are going to require that students spend countless hours working on a capstone engineering project to get their accredited degrees, we might as well put them to work on a problem that matters to society, and make sure that their work actually helps solve the problem. Along the way, we might teach them what it takes to keep a design history file, conduct a clinical trial, or properly document a manufacturing process to maintain FDA standards.

There is work to be done in creating and using an open, model process for creating an FDA-approved product that would otherwise never be created, in order simply to show others the way that such a process should be run and documented. Imagine the excitement of community college technology education students participating in machining and assembling parts for a prosthetic arm prototype designed by an engineering undergraduate, supervised by an engineering management or business school graduate student with experience in the medical device industry, all as part of a documented FDA-compliant process.

Liberating Technologies, Inc.
325 Hopping Brook Road
Holliston MA 01746-1456

7 September 2009

To whom it may concern:

I am the Director, Product Design, for Liberating Technologies, Inc. (LTI). Our company is an off shoot from a research project at the Liberty Mutual Insurance Company Research Center that began in 1973, but in 2000 LTI became a separate company. Most of our personnel date back to the previous team at Liberty. For thirty years, we have designed and distributed upper extremity prosthetic components. LTI manufactures the Boston Digital Arm, the only commercially available product that can monitor and control 5 motors and their associated control channels. LTI also imports and distributes a wide range of orthotic and prosthetic products.

Due to LTI's interest in controlling multiple devices, I proposed in 2002 that a task force be set up to write the specifications for an open-source industry-wide standard for using a bus to communicate between multiple devices. A researcher in Norway agreed to try to coordinate the efforts of the many groups that supported this effort at the initial meeting at the University of New Brunswick. This effort foundered when funding did not materialize.

When the open-source bus was proposed, there was only a little research activity in upper extremity prosthetics. Since then a number of new players have entered both on the research and development side, sponsored by DARPA, and on the commercial side with the advent of the ILimb Hand. Now, instead of only three or four degrees of freedom, people are talking of controlling 20 or more. Furthermore, there is now a major effort to use pattern recognition to squeeze more control information out of muscle signals. For instance, at the present time there are subjects who can control three or more functions in both directions with only three muscles. And they can do so in a natural way by attempting to do with their bodies what they did prior to amputation.

With an open-source bus, one manufacturer can develop the ideal signal processor while others develop hardware to use the control information generated. This effort will only succeed with a common control bus to move information from the source to the output devices.

At present there are several research efforts all implementing different digital standards for prosthetic arm component control, some of these are leading to products that are intentionally incompatible with the products of competitors. These initiatives will serve to further segment an already very small market, reducing choice for consumers and reducing market share for smaller manufacturers such as LTI. Many of these efforts have been almost wholly funded by US Government money, including the funding for the commercialization efforts.

The U. S. government is in an ideal position to push the industry toward a standard bus. Both of the current DARPA arm research projects use the automotive CAN bus standard for communication, but they are not yet compatible with each other. Further, one of these projects involves a foreign manufacturer large enough to block further innovation in this field if it uses a non-standard bus with the commercial version of the devices. LTI believes that government sponsored research should benefit large a number of companies as possible. With an open standard, LTI and the other small, innovative groups in this country can concentrate on designing components and control modules that will benefit amputees everywhere.

As the person who initially proposed an open standard, I am willing to help in any way possible to see that the research now being sponsored by our government leads to products that benefit as many amputees as possible. I would like to see the United States get its share of the world prosthetics market, and an open bus standard will certainly help us to do so.

Respectfully,

T. Walley Williams, III
Director, Product Development
[redacted]

September 8, 2009

To whom it may concern:

As the President of Motion Control, a manufacturer of powered arm components, including the Utah Arm elbow, electric hands, and the Electric Terminal Device (ETD) electric hook. Currently, our components are generally compatible with those of other manufacturers through an analog connection and control standard that has been used by the industry for a few decades.

It is becoming clear that for successful integration of electronic devices we all can foresee for the future, digital communication will be necessary. We think it will be important that future developments adopt a common communication standard, so that future components can all "talk" to each other, and allow consumers to choose components from all manufacturers. This standard is especially important for efforts which are
funded by the US Government money. We feel that the recipients of government funding for prosthetic component development should adhere to an open control standard for products created using those funds – the result will be a net lower the cost of innovation, and greater choice in the marketplace. This is more than just consumerism – this actually can effect the rehabilitation of persons with severe life-long disabilities.

As an example, both of the current DARPA arm research projects use the automotive CAN bus standard for communication – i.e., the hardware is there, but the two projects are not yet compatible with each other. By following an open standard these newer developments would more likely be compatible with each other, as well as with new products developed by other US developers in our industry.

Open architecture for prosthetic arm control is a good idea for consumers, and a good idea for most manufacturers.

Yours truly,

Harold H. Sears

Harold H. Sears, PhD
President
Motion Control, Inc.

JOHN CUMBERS

Dec 6, 2011
John Cumbers, Ph.D
[redacted]

December 6, 2011
OSTP, The White House

Dear OSTP Bioeconomy RFC,

I commend your call for input to the National Bioeconomy Blueprint. I have a M.Sc in Bioinformaitcs (Edinburgh University) and a Ph.D in Molecular Biology (Brown University). I have been involved in the field of synthetic biology since starting the Brown iGEM team in 2006.

I founded and run the BioSysBio conference in synthetic biology, co-founded the synthetic biology company Universal BioMining and have recently co-founded a synthetic biology incubator called SynBio.me in Silicon Valley. I also work at NASA Ames Research Center and help to run the synthetic biology program there.

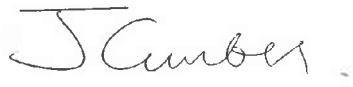
I have a simple message:

1) The academic education system does not scale well. There are few formal education mechanisms for the bioeconomy outside of the Ph.D system. The Ph.D system is an antiquated apprenticeship and is ill-suited to supply the labor needed for the coming bioeconomy. Radical alternatives should be experimented with.

2) The development of ideas could be facilitated by low cost, well equipped and well funded public labs where researchers having new ideas can bring them to fruition without the formal structure of an academic institution. Lab benches should be able to be rented per researcher per month at a low cost.

3) One grand challenge to consider is the $1000 genome. Not sequencing, but synthesis of an entire bacterial genome for less than $1000.

Sincerely yours,



Sincerely yours,

John Cumbers

NEW MEXICO STATE UNIVERSITY RESPONSE TO OSTP FOR REQUEST FOR INFORMATION FOR NATIONAL BIOECONOMY BLUEPRINT

While the following considerations were developed to address challenges in technology transfer in university settings, they apply generally to broader settings of making the products of basic science marketable and specifically to the life sciences, which share a number of traits with university-developed innovations. In both cases, thoughtful strategies are needed to advance early-stage, high-risk technologies in challenging financial landscapes.

In April 2011, the National Advisory Council on Innovation and Entrepreneurship (NACIE), a subgroup of the U.S. Department of Commerce's Office of Innovation and Entrepreneurship, published a response to a request from then-Secretary of Commerce Gary Locke, who had charged members of NACIE with devising policy recommendations to "facilitate economic growth through entrepreneurial activity, the commercialization of new ideas and technologies into high-growth, innovation-based businesses, and job creation" (www.eda.gov/NACIE). NACIE's initial reply, *Letter to Secretary Locke: Recommendations to Facilitate University-Based Technology Commercialization* was followed by a more comprehensive *Report to Secretary Locke: Improving Access to Capital for High-Growth Companies* (June 2011). The majority of the material in the following sections is derived from these publications.

Moving life science breakthroughs from lab to market:

What are the barriers that keep medical breakthroughs from coming to market in a reasonable amount of time? Can federal agencies alter present practices to ensure treatments come to commercial markets more quickly? Would changes in the Small Business Innovation Research (SBIR) or Small Business Technology Transfer (STTR) programs alleviate some of the recognized barriers? Are there alternatives to the dominant venture funding model? If so, do such alternatives feature a role for government agencies?

U.S. researchers continually produce world-leading innovations in the life sciences. The expertise to develop these innovations, however, is just one component necessary to advance new products to commercial markets. Presently, medical breakthroughs take too long to reach market and the process for commercialization is too variable. Linear models whereby federal funds underwrite purely scientific research resulting in engineered solutions to medical challenges, which must be patented before testing, production, and distribution is not sustainable. In some cases, the original challenges have fundamentally changed before bioengineered solutions can arrive on markets. In others, the cost of RDT&E with flawed intellectual property management discourages firms from investing in the first place. While funding and support for basic research is essential, continued and expanded access to resources for other components of commercialization are equally imperative. The primary barrier to technology transfer is lack of a process that incorporates commercial concerns from the start of research development, as well as a lack of dedicated resources to support and sustain that involvement.

Successful commercialization activities depend upon concerted collaboration by stakeholders from a range of backgrounds: researchers, technology transfer professionals, legal experts, business and marketing specialists, industry representatives, entrepreneurs, investors, government bodies, and economic development organization agents. Creating opportunities for these parties to closely work together throughout the innovation development process and incentivizing technology transfer activities for all involved is essential.

Several strategies have been recommended to universities to facilitate this sort of engagement. Institutions are encouraged to not only promote the importance of technology transfer, but also to encourage participation in related activities by incentivizing researcher involvement in commercialization (which is rarely incorporated in faculty promotion and tenure policies). Universities are also urged to make reporting and compliance obligations as simple as possible, to allow funded researchers to devote their time to other activities. While the reporting requirements for federally-sponsored programs vary by agency, and these requirements pose significant time staff, time, and resource challenges, examining ways to streamline these practices would be worthwhile. Further, institutional policies that create friendly environments for researchers and others engaged in the commercialization activities can help pave the way for new and enhanced streams of revenue.

One of the most powerful drivers of successful commercialization is the establishment of policies and programs that foster productive partnerships between researchers and industry. Many universities are engaged in the development and expansion of initiatives that facilitate industry access to university expertise and resources. One aspect of these efforts is creating spaces and events in which current and potential partners can meet, both informally (e.g., sponsored professional conferences and networking events) and formally (e.g., shared laboratories and facilities, student-faculty-industry research teams working on common goals, and research parks). Another is focused funding of program models that develop and advance technologies based on market pull research and establish early-stage relationships between university and industry partners (e.g., proof of concept programs). Specifically, systems that provide joint access to federally-funded intellectual property can prove extremely successful in merging the interests of researchers and industry partners.

Similarly, the adoption of supportive government policies and agendas can help to address commercialization challenges. Entrepreneurs are the engine of economic growth; those engaged in high-risk potentially high-reward research are the key. Large institutions, both corporate and academic, might not have the flexibility take such chances. Individual faculty members or those in small groups are more likely to succeed. However, efforts by individuals or very small groups are not sustainable . One of the best ways federal agencies may provide support is through the addition or enhancement of collaborative commercialization-supportive components in funding opportunities. For instance, greater inclusion of commercialization plans in proposals and deliverables will both emphasize the importance of these factors in funded research and provide

resources to allow awardees to devote adequate time to plan and execute related activities. Similarly, incorporating market potential evaluation as an early-stage milestone in research benchmarks can help to ensure that researchers keep commercialization considerations in mind and will help to quickly identify those innovations with significant market potential and those which may fall short. Above all, federal assistance in subsidizing early-stage technologies in ways that best mitigate the risks associated with such projects is crucial.

SBIR and STTR programs are among the best examples of this type of funding. While these grants provide researchers strong support as currently structured, modifications to these models could enhance them as drivers to commercial success. One possibility is incorporating into the current SBIR/STTR structure (i.e., Phases I, II, and III) a "Phase 0," which could be used by universities and other institutions to fund commercialization-supportive activities such as developing prototypes, identifying and compensating mentors, and devoting time to assessing market readiness of emerging technologies. Additionally, streamlining the SBIR/STTR approval timeline could be extremely helpful to applicants and awardees. Presently, the average wait time of 6-12 months from application submission to notice of award can be detrimental to researchers and partners attempting to launch start-ups and facing severe financial constraints. Reducing the approval process to, ideally, three months would give awardees a chance to better address gaps in capital that can limit, or even end a project. Additionally, changes to existing phases could be beneficial. For instance, Phase I funding guidelines could incorporate a voucher requiring a dollar-for-dollar match from a private sector partner before it could be cashed in. Grantees could be required to locate in or to contract with a research university. Federal funds could be made available for Phase III grants, ensuring that ventures with strong foundations are not left stranded after significant investment of resources and allowing them to take the final, crucial steps to market.

Public-private partnerships:

What are successful models for public-private partnerships? What would public-private partnerships in the bioeconomy look like, and what goals would they pursue? What opportunities exist for collaboration in the pre-competitive space, and is there a role for government here?

The federal government can play a significant role in shaping favorable environments for public-private partnerships. A number of excellent existing programs serve as models in this arena. For example, the National Institute of Standards and Technology's Advanced Technology Program (ATP) provides public-private partnering opportunities for universities, non-profits, and companies at all stages of development. Its focus on industrial technology needs emphasizes the importance of market-based, demand pull research effectively merges the needs of private industry with the expertise of public institutions. Employing this model in federal initiatives, such as the EDA's plans to focus on regional innovation clusters (RICs) to stimulate economic growth and create jobs, will serve to extract the greatest benefits from all programs. By making

procedures and processes as efficient as possible for partners at all stages of development, the federal government can ensure the strongest collaborative efforts.

NACIE provides recommendations for both early and later stages of high-growth initiatives. The first early-stage recommendation is providing refundable tax credits for individual angel investments, a program with demonstrated success in pilot markets (e.g., British Columbia). Safeguards in such an initiative, such as limiting the program to those investing in accredited Qualified Small Businesses, would offer greater chances of successful ventures. Second, extension of capital gains tax exclusions outlined in the 2010 Small Business Jobs Act could lead to greater investment in early-stage Qualified Small Businesses. Additionally, an extended nine-month rollover period on capital gains could lead to later-stage investments. Third, implementing a100% exclusion on corporate income taxes for Qualified Small Businesses in their first year of profitability and a 50% exclusion on the following two years of profitability could create a safety net in early stages and augment capital for later investment in the venture. This recommendation is noted by NACIE to have significant potential impacts in life sciences research and commercialization, where technologies typically require much longer development times to reach marketability. Fourth, as noted above (see response to "Moving life science breakthroughs from lab to market), shortening average approval times of SBIR/STTR grants would make the awards better-suited to the considerable early-stage capital needs of high-growth projects. Fifth, amending current Small Business Investment Companies (SBIC) program regulations to allow for a reduced approval process and interest rate payment reductions, along with expanding eligibility to certain angel investment groups, micro-VCs and venture development organizations (VDOs) could greatly impact private sector interest in high-growth investments.

NACIE also provides three recommendations for improving later-stage access to capital for high-growth companies, ensuring that the resources invested in launching a venture are well-spent as the project is allowed continued growth. First, the government should commit to sustaining current capital gains tax levels at 15% for funds invested in businesses, rather than following through with increases mandated by Bush Tax Cut expirations and Patient Protection and Affordable Care Act. This could mitigate risks of venture capitalists considering investment in high-growth firms, whose returns on investment would be negatively affected by these tax increases. Second, the U.S. Securities and Exchange Commission (SEC) is encouraged to mediate in the Spitzer Decree, which prohibits use of investment banking revenue to cover costs of market research in start-ups. This type of research is essential to spark investor confidence and is necessary to successfully execute IPOs needed for continued funding. Finally, NACIE recommends mitigation of Sarbanes-Oxley obligations for smaller public firms, allowing these organizations greater freedom in raising later-stage capital through public stock offerings

In planning future initiatives for enhancing public-private partnerships, it is beneficial to consider past successes and build on these models. A prime example in this area is the work of the late Dr. George Kozmetsky, who, in 1977, founded the IC^2 Institute at the University of

Texas at Austin. Through collaboration with partners such as the Austin Technology Incubator, the Bureau of Business Research, and the Global Commercialization Group, the IC^2 Institute continues to affect the convergence of knowledge and technology transfer. Similarly, NASA's Commercial Technology Network supports an array of programs that assist start-ups built around NASA technologies to develop into stable businesses. With Field Centers, Regional, and National Technology Transfer Centers, the program has a searchable TechFinder database for potential collaborators and an impressive record of successful partnerships.

December 6th, 2011

Megan J. Palmer, Ph.D.
Department of Bioengineering, Stanford University
Synthetic Biology Engineering Research Center (SynBERC)
[redacted]

Office of Science and Technology Policy
Executive Office of the President
725 17th Street Room 5228
Washington, DC 20502

Re: OSTP Request for Information: *Building a 21st Century Bioeconomy*

Dear Office of Science and Technology Policy,

I am a Postdoctoral Scholar in the Department of Bioengineering at Stanford University and serve as the Deputy Director of the Practices Thrust of the NSF Synthetic Biology Engineering Research Center (SynBERC). This response to the OSTP's Request for Information on *Building a 21st Century Bioeconomy* focuses on the role that synthetic biology and its practitioners can play in shaping the bioeconomy. Synthetic biology tools and techniques - when developed alongside an understanding of their societal ramifications - offer tremendous potential to accelerate the development of a bioeconomy that improves livelihoods in the US and abroad. Specifically, the recommendations herein focus on **critical needs to develop people, programs and places for addressing gaps in creating sustainable biotechnological solutions for economic, social and environmental needs.** These recommendations reflect views collected and developed via my continued interactions with SynBERC-affiliated researchers and partners in academia, industry and other organizations, in particular members of the SynBERC-supported Synthetic Biology Practices Working Group (SBPWG). The SBPWG, which I lead, is a diverse group of synthetic biology community members interested in advancing best practices for the responsible development of biotechnology. We strongly support your efforts to develop a national bioeconomy blueprint and urge you to consider integration of these recommendations and approach us for additional consultation.

SynBERC, the SBPWG, and the synthetic biology community at large, strive to enable predictable, reliable, sustainable and cost efficient engineering of biological systems. Synthetic biology tools and techniques – including standardization of parts and processes for genetic engineering, creation and characterization of novel biological functions, and design of synthetic organisms – can drive the industrialization of biology for existing and new application areas. Developing these technologies in concert with an advanced understanding of the factors affecting how technologies manifest in the world will inform design and implementation that is more efficient, effective and well-matched to areas of need and opportunity.

Synthetic biology is now starting to deliver on its promise. For example, recently we have seen the development of a bacterium with a synthetic genome by the J. Craig Venter Institute, the

production of an antimalarial drug precursor via engineering of yeast metabolic pathways by Amyris Inc., the distribution of free-to-use sequence and functional expression information for collections of standard genetic elements by the BIOFAB, and the use of standard genetic parts to design and build living systems by over 160 undergraduate teams at the yearly international Genetically Engineered Machine (iGEM) Competition. Yet these and similar achievements continue to raise many challenging questions about how biotechnology can be effectively channeled to create economic, social and environmental value. For example:

- What application areas are most economically viable for developing and deploying biology-based alternatives to current manufacturing platforms?
- What are appropriate criteria for evaluating safety and efficacy of new 'intrinsic containment' strategies – such as the use of non-natural genetic codes – across various application areas?
- What property rights structures for uses of genetic functions might best support innovation?
- What are effective and appropriate strategies for proactively identifying and responding to potential dual-use biotechnologies in early stages of research design and implementation?

Answering these types of questions – and many others – requires a **systemic promotion of interdisciplinary training, research and development efforts**. I outline three critical areas for which we can develop support for interdisciplinary inquiry – **education (people), research (programs), and venues (places)** – but emphasize that all three areas are inherently coupled and mutually reinforcing.

People: Interdisciplinary Education and Training in Bioengineering and Interacting Disciplines

Effective development of a bioeconomy will require technology leaders able to cross traditional disciplinary boundaries to address opportunities and confront challenges which have non-technical dimensions. Until biotechnologies establish more rigorous standards of practice, much of the emerging bioeconomy workforce will continue to train in American research universities, largely at the graduate level. Currently there is little exposure within university training to practices in technology development beyond academic labs that could equip practitioners to effectively frame their work with a translational focus. We cannot expect researchers to inform their design to meet anticipated needs for production and scale-up, or provide advice on high-level policies for biotechnology, without themselves or their mentors receiving training or exposure to real-world criteria and practices.

We advocate promotion of university programs in bioengineering that leverage existing expertise in industry and government, and increase interactions with other disciplines. We would also encourage opportunities for students in other disciplines, such as law, business and social sciences – to learn about biotechnology. A bioeconomy blueprint should encourage and facilitate the restructuring of relationships to prepare students to creatively, strategically, and responsibly develop biotechnologies.

While there is no single solution, there are many existing strategies that can be further developed to bridge educational gaps:

Professors in Practice: University faculty positions targeted at veterans of industry and government that can provide complementary teaching and research project advisement alongside traditional academics
Internships / Co-ops: Undergraduate and graduate fellowships / programs requiring internships in industry and/or government
Interdisciplinary Programs: Graduate fellowships / programs targeted at interdisciplinary research (e.g. bioengineering alongside economics, law, ethics, risk management, etc.)
Design Courses: Undergraduate and graduate design courses in which teams of students from across disciplines work on projects solicited from, and advised by, industry clients
Short-Courses in Topics of Practice: Workshops engaging practicing scientists and engineers on topics complementing their work, such as science and technology policy
Bioengineering for Non-Bioengineers: Outreach programs introducing bioengineering principles to students outside of bioengineering to engender future interdisciplinary research opportunities
Professional Societies and Accreditation: Creation and support for organizations developing professional standards and accreditation in bioengineering practice
International Students: Visa and immigration reform allowing the US to attract and maintain the best young minds from around the world

There is also a complementary need to develop appropriate metrics and critical success factors to be used to evaluate the effectiveness of these programs in preparing students for diverse career paths.

Programs: Funding Interdisciplinary Research and Facilitating Industry and Government Partnerships

Solutions to pressing challenges in biotechnology development often remain unaddressed because they fall between interdisciplinary boundaries and require input from partners outside academic institutions. Many barriers exist to effectively pursuing interdisciplinary work within universities, including the simple fact that most academic researchers, as outlined above, are never trained to frame interdisciplinary problems. They are therefore not likely to value, nor engage in, interdisciplinary pursuits independently, or inspire their students to do so. Furthermore, many of these potential research problems don't fit squarely within current funding programs, disciplines, or academic departments. We recommend promoting research funding programs, and institutional restructuring, which incentivizes collaborations between researchers with complementary disciplinary expertise, and partners from industry and government. These programs would examine biotechnology development from a comprehensive engineering systems perspective. We also recommend exploring opportunities for facilitating public-private partnerships, including evaluating successes and challenges within existing programs (such as NSF ERCs) designed to engage industrial partners in framing projects towards a translational focus. Specifically, there is a need to evaluate the effectiveness of these programs for developing 'horizontal' technology platforms versus 'vertical' application areas for biotechnology.

Places: Venues for Interdisciplinary Collaborative Research Programs

Enabling interdisciplinary and translation-oriented research requires venues which co-locate heretofore disparate researchers and partners to effectively collaborate to frame and work on projects. Venues would ideally bring academic, industry and policy practitioners together to rapidly prototype the development of biotechnologies as well as the practices and policies

coupled to their successful translation. The BIOFAB, located at the Joint BioEnergy Institute (JBEI), provides one example of an innovative approach in which a professional team of researchers are piloting the development and dissemination of free-to-use sequence and functional expression information of standardized genetic architectures. The BIOFAB team must confront not only technical challenges, but also challenges relating to standards, property rights, business models, industry partnerships, and security. The National Labs provide fruitful places to build upon existing expertise in mounting large coordinated projects, and should therefore be examined for missed opportunities to build partnerships with industry, and create closer ties with policy experts.

Through promotion of coordinated efforts enabling interdisciplinary training, research and development across these three critical areas – people, programs and places – I strongly believe we can more effectively realize a *21st Century Bioeconomy*.

Please feel free to contact me for clarification or further comments.

Sincerely,

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Acknowledgments: Members of Synthetic Biology Practices Working Group (SBPWG) made significant contributions to this letter, including notably Joshua J. Wolf, Andrew Chang and Jay W. Vowles, all in the Department of Bioengineering at Stanford University.

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To: The Office of Science and Technology Policy

From: The Enzyme Function Initiative, a National Institute of General Medical Sciences Large Scale Collaborative Project (U54GM093342)

Response to the Office of Science and Technology Policy's RFI on Building a 21st Century Bioeconomy

December 2011

The Enzyme Function Initiative (EFI) has prepared this statement in response to the OSTP's RFI on the Obama Administration's National Bioeconomy Blueprint. As a large scale collaborative grant addressing a major challenge in contemporary science, deciphering enzyme function, the EFI believes supporting research and development themes that tap into the tremendous information generated by high-throughput genome sequencing will be critical for significant advances in human health and productivity.

The EFI is a Large Scale Collaborative Program (also referred to as a "Glue Grant") supported by the National Institute of General Medical Sciences (NIGMS; U54GM0933342). This recently retired program focused on promoting integrative and collaborative approaches which are increasingly needed to solve complex problems in biomedical science. The EFI was awarded in May 2010 to develop a robust sequence/structure-based strategy for facilitating discovery of *in vitro* enzymatic and *in vivo* metabolic/physiological functions of unknown enzymes discovered in genome projects, a crucial limitation in genomic biology. This goal is being addressed by integrating bioinformatics, structural biology, and computation with enzymology, genetics, and metabolomics.

It is our understanding that the purpose of the RFI is to solicit input on research and investments that will substantially contribute to the US bioeconomy, with a specific directive to comment on multidisciplinary funding efforts that would revolutionize the prediction of protein function for genes. As a dynamic collaboration of researchers devoted to this very goal, the EFI is uniquely qualified to provide perspective on this issue.

In this statement, we recommend OSTP urges the Administration to:

- Support research to develop more sophisticated protein classification algorithms
- Support research aimed at developing platform technologies that would enable accurate large-scale *in silico* docking of metabolites with both experimentally determined crystal structures and homology modeled structures
- Support more multidisciplinary collaborations between experimental groups and computational groups
- Support a comprehensive public database of functional data
- Develop a program promoting and ensuring the success of multidisciplinary collaborations

Current State of Enzyme Functional Annotation

The "genomic age" saw the sequencing of the human genome along with the genomes of hundreds of other eukaryotic and thousands of prokaryotic organisms. As of June 1, 2011, the TrEMBL database contained 16,014,672 protein sequences, up a staggering 47% from 10,867,798 just one year earlier in June 2010. Despite this explosion in genomic knowledge, many of the protein sequences in the databases have uncertain, unknown, or incorrectly annotated functions. Without correctly annotated

functions, the tremendous utility that the newly discovered enzymes and associated metabolic pathways could provide to advance medicine, chemistry, and industry will go unrealized.

With improvements in sequencing technology, the cost for sequencing a 4 Mb genome is now ~$10K and decreasing, with the implication that the number of protein sequences will increase indefinitely. For example, deep sequencing technologies are being applied to populations of closely related organisms, including medically important strains of pathogens. As the focus shifts to leveraging these data to discriminate differences between pathogenic and benign strains, the need for reliable functional assignment has become acute, requiring the development of effective approaches for functional assignment of unknown enzymes and pathways.

Challenges to Large Scale Annotation

Existing strategies for functional assignment of unknown proteins utilize clues from sequence similarity analysis, operon/metabolic context, and phenotypic/transcriptional profiling, as well as other approaches. In the case of enzymes, although these approaches may provide functional clues, e.g., the enzyme is a kinase or an aldolase, they rarely define the identities of the substrates and, therefore, the molecular functions. Furthermore, these strategies are by and large extremely low-throughput and efforts to extend this approaches to large scale analyses are either non-existent or in initial stages of development.

New orthogonal approaches for predicting the substrate specificity of unknown enzymes are needed that provide a general, more direct method for functional discovery. To be effective, new approaches must incorporate high throughput predictive methods to focus and enable the more time-consuming experimental assignment of function. However, the necessity of these approaches has come into focus only within the past few years, and the full scope of the functional prediction challenge is just now crystallizing. In essence, progress towards this goal is in it's infancy. Although efforts such as the EFI and attention such as this RFI is moving the issue of prediction of protein function into the public eye, it is clear that considerable investment from the bioinformatic, computational, and biochemical communities is needed with requisite support from funding agencies.

Recommendations

1. Support research to develop more sophisticated protein classification algorithms

Public sequence databases are currently flooded with misinformation. Developing automated algorithms that more accurately classify proteins (and therefore the likelihood of a given protein's physiological function) is critical. Ultimately, classification algorithms should be utilized retrospectively and prospectively on the sequences deposited in public databases to correct past misannotation and avoid future misannotation. Fulfillment would provide the biomedical community with more meaningful upfront estimates of protein function.

2. Support research aimed at developing platform technologies that would enable accurate large-scale *in silico* docking of metabolites with both experimentally determined crystal structures and homology modeled structures

Generation of quality templates for docking and evaluation of results is both computationally intensive and requires careful, skilled, and therefore low-throughput, human intervention. However, to achieve large scale predictive power, support for automated utilities is needed. Ultimately, such utilities would be open source and provide results scored in a format that would allow facile evaluation (e.g. via a graphical output and probability score akin to the E-value). Fulfillment would provide the biomedical community with the ability to generate and evaluate higher quality predictions of protein function.

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3. Support more multidisciplinary collaborations between experimental groups and computational groups

Without experimental testing on a subset of computational predictions, the algorithms are unvalidated and their value is nebulous. The importance of pairing experimental and computational groups to develop, test, and refine computational methodologies cannot be overstated. Productive collaborations, especially across disparate disciplines, takes considerable investment by both the researchers who must establish and maintain the partnership and also by the granting institutions who must support such collaborations despite an increase, albeit modest, in the expenses required to effectively carryout the project (e.g. travel, conferencing options, etc). Fulfillment would provide the biomedical community with significantly increased confidence in predictions of protein function.

4. Support a comprehensive public database of functional data

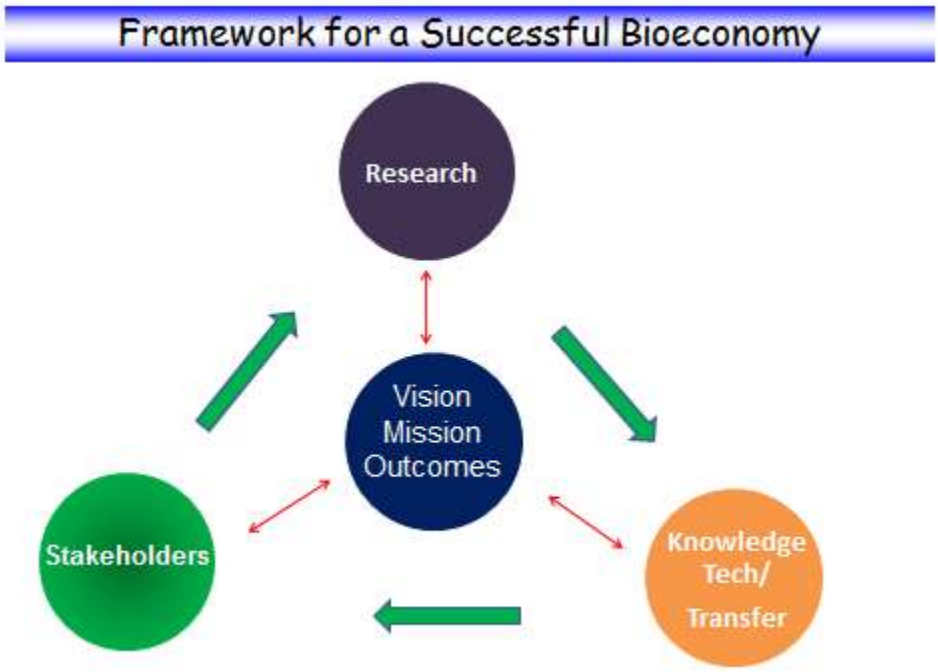
As the number of sequenced genomes has grown, functional information on a fraction of the resulting proteins has also increased. However, there is no comprehensive repository to make the full spectrum of functional data from all experimental, informatic, and computational disciplines accessible. This barrier creates an environment where research is done in isolation with piece-meal information and little large-scale context. Ultimately, a central functional database, ideally linked and/or incorporated into current sequence databases, would be developed. Fulfillment would provide the biomedical community with comprehensive access to evidence of protein functions.

5. Develop a program promoting and ensuring the success of multidisciplinary biomedical collaborations

Progress on any scientific theme of wide scope and complexity demands integration of many disciplines. The EFI's experience is that collaboration on this scale is in itself an experimental science. A centralized program that provides guidance and support for establishment and management of large-scale multidisciplinary collaborations would dramatically increase the efficiency and productivity of such efforts. Fulfillment would ensure the biomedical community receives the maximum benefit from the funding invested.

Concluding Remarks

While the EFI is developing one strategy to predict protein function in functionally diverse enzyme superfamilies, it is only one among the many multidisciplinary efforts needed to address this issue. However, with support for biomedical research increasingly challenged by budgetary constraints at NIH, large-scale grants have been targeted as too costly to maintain, and very few opportunities now exist to solve problems as complex as prediction of protein function. To truly make use of the enormous potential that sequenced genomes hold, quality functional predictions must be generated, validated at least in part, and disseminated. This requires dedication by the scientific community to focus a significant amount of research effort on functional assignment and also requires commitment from funding agencies to invest the requisite resources to accomplish meaningful goals in this area.



In the recent multiagency report *The Future of Biology* the authors noted that, while physics shaped the 20th century, biology is already and will continue to shape the 21st century. However, while there is justifiable optimism about the capabilities in this arena, especially where it interfaces with other disciplines to provide innovative solutions to real world problems, many challenges still exist before the bioeconomy can begin to deliver transformative, scalable, sustainable outcomes that will form the basis of our future prosperity.

As the US struggles to retain its leadership position in the life technologies field, in addition to promoting cutting edge science and technology transfer it is also vital that programs are supported to provide a source of highly trained, exceptional quality scientists. The confluence of IT, physical sciences, engineering and life sciences is creating dynamic new technologies that are principle drivers of the bioeconomic industry. The more we focus in this space, the more successful the US will be in contributing to knowledge generation, job growth and economic viability for the nation.

(1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, nonprofit organizations, foundations, and other stakeholders to achieve this goal. Research and development: R&D investments, particularly in platform technologies, can support advances in health, energy, the environment, and agriculture, and accelerate the pace of discovery in fundamental life sciences research.

While we appreciate that the focus of this RFI is translation of life sciences research into commercial products and human capacity building we consider that it is appropriate to

comment on a number of general issues that apply across the board to all scientific and technological research. The challenge for research institutions is to find the balance on the spectrum from the most basic enquiry-driven research to the most applied mission-oriented investigation. While the latter is closer to the expressed intent of the RFI, it is crucial not to lose sight of the fact that basic knowledge-focused enquiry is the foundation for transformative research. The further down the spectrum one progresses, the more incremental and less impactful the research becomes. The US cannot afford to burn its seed corn by being too prescriptive in its determination of what will have the greatest contribution to the bioeconomy. Prioritization must be a balance of short term quick-to-commercialization efforts balanced with longer term riskier research as the latter is the area from which the greatest payoffs will come. In most instances, ROI in such research is not a quick delivery - transformative research is not incremental but saltatory so there needs to be a commitment to adequate investment in this space to support creative high risk/high reward research which is crucial to building the foundation for a thriving economy in the long run. It is illustrative of the value of long term investment that a number of today's leading technologies and top jobs did not exist 10 years ago so being too prescriptive would be an imprudent move. To not lose the opportunity of capturing the most creative ideas the various agencies should make sure that program managers use the most effective tools in the selection of reviewers and in the merit-review process to ensure that prospective transformative ideas are not lost in the mundane. There are few of us possessed of sufficient wisdom to predict the future but we can anticipate future needs and not develop outmoded products or train a workforce with obsolete skills.

There is a need, however, for the NSF/NIH funded coterie of strong basic researchers and research platforms to join together and build substantive funding that supports research beyond the exploratory stage to proof of principle. The agencies should create new interdisciplinary opportunities that are not perceived to exist presently. Such gap funding will allow investment in translational research that moves discoveries from the lab to commercial production. Caution is advised though to not create too much mission creep and to ensure that excellence always prevails at every point on the continuum. Countries that have hit the right balance such as Finland, South Korea and Singapore, continue to thrive despite the global economic downturn. They invest between 3 and 5% in research and no other countries have prospered without healthy investment in this sector.

Below we outline a number of key opportunities and challenges to achieving the promise of the bioeconomy. Since, no doubt, you will receive many submissions and redundancy is inevitable (as is the case in all robust biological systems!) we will attempt to focus on a number of key areas where we believe our institution shows exceptional strength and promise. These are an outline of some potential areas not well served by current funding sources with the potential to be transformative within the Life Sciences interdisciplinary sphere. These examples represent major themes including broad scope technologies and important challenges. They range from somewhat prescriptive to open-ended and are not meant to be exhaustive or comprehensively outlined but to indicate opportunities.

Holistic Health

The term "health" should be all encompassing from the meta-level of the planet and all its myriad networks to the micro-level of the subcellular including the complete spectrum of life writ large between. To achieve this aim there should be multiagency, multidisciplinary funding efforts pitched at a global scale to support research into the ultimate grand challenge of our times which is nothing less than the sustainability of the Biosphere and our place in it. Jorgensen (2011) poses the ultimate question - can we learn how to meet our needs today without compromising the ability of future generations to meet theirs? Obviously this is too large a question to address in one sweep but it can be subdivided into more manageable components. We must establish structures to help design the multi-investigatory integrated tool box of the future to find answers to the overarching questions of how life exists and thrives from the subcellular to the global level. At UC Davis we are developing a One Health approach that looks at the intrinsic and extrinsic interactions that underpin global health from the environment to the myriad organisms it supports.

Jorgensen RA (2011) We're all computational biologists now…next stop, the global brain? Front. Gene. 2:68. doi: 10.3389/fgene.2011.00068

Platform Technologies

To provide answers to this overarching issue of global health, the bioeconomy must address fundamental challenges that cut across all disciplines and would qualify as a unifying grand challenge.

Large Data Management

One of the greatest challenges that requires a platform solution is how to adequately curate, manage and mine the tsunami of data that the tools of modern biology generate in an ever growing surge. The massive volumes of data however are not just being generated from genomics research but across multiple technology platforms (sequencing, genome-wide-studies, imaging, microarrays, proteomics, metabolomics, lipidomics, glycobiomics, tissue maps) and are now beyond the reach of most researchers, so that every day they make decisions on everything from experimental design to clinical trials based on inferior or incomplete information sets because they lack the ability to harness the power of the big data sets that inform their areas of interest.

The ultimate goal of biological research is to enable the discovery of new insights as well as to create a global perspective from which unifying principles in biology can be discerned. There are three important sub-disciplines within the life sciences informatics: the development of new algorithms and statistics with which to assess relationships among members of large data sets; the analysis and interpretation of various types of data across datasets, including nucleotide and amino acid sequences, protein domains, and protein structures (the so-called semantic web); and the development and implementation of tools that enable efficient access and management of different types of information stored in many types of formats (the meta web). UC Davis has the expertise and capability to develop and apply the computational tools necessary to address these challenges and extract and convert useful information into enabling technologies that can

apply to such actions as finding and introgressing novel traits in plants and animals to respond to changing stressors and optimize quality and productivity, or designing novel biomarkers for assessing individual response to, and anticipation of, nutritional and disease states. University/private sector collaborations are best suited for such applications. The UC Davis Genome Center (GC) faculty provides numerous opportunities for multidisciplinary collaborative genome-scale research. The GC provides leadership through focus groups in epigenetics and networks biology, and, currently in protein-structure function and metagenomics. New scalable capabilities will also now be provided by the on-site computational power of the Beijing Genome Institute.

High Content Analysis

Beyond high throughput screening, new toolsets are needed for R&D applications which have proven inadequate, such as measuring multiple biological pathways simultaneously, or revealing off-target drug effects. Novel tools need to be developed at the convergence between cell-based assays, high-resolution fluorescence imaging, automated and advanced image processing and analysis software for target identification and validation and to provide secondary screens to elucidate a drug's mechanism of action or to reveal undesired effects such as potential toxicities or counter indications. We are now moving towards a metagenomic view of drug metabolism. There are few support options in public institutions for this type of mission-oriented research. Novel bridging grants or fund matching challenges with industry for the more applied side of this research would help advance the understanding and development of suitable intervention protocols and perhaps speed up the clinical trial process.

Deconvoluting Complexity

One of the most important problems of the 21st century with respect human health is how to translate complex high dimensional "-omics" data into workable solutions to inform clinical applications, personalized medicine, nutritional genomics and lifestyle choices. As our knowledge of multidimensional networks increases we begin to see that network perturbation rather than single gene effects is the principle underlying cause of many diseased states, whether referring to plants or animals, and especially the Homo sapiens subset. However, the majority of therapeutics is designed to target single proteins/receptors. The FDA clinical trial process is designed to test single drug effects and has no capacity for testing the more effective multiple interaction synergistic approach to therapeutic development that promises to be the most effective medicine of the future. With more effective modeling systems such as, for example, topology of protein-protein interaction networks, it is possible to develop methods that can explicitly model the possible synergistic effect of drug combinations to target multiple proteins in diseases such as cancer. Also the use of semi differentiated stem cells could potentially speed the upfront pre-clinical bottle necks and obviate the need for many animal trials. This could inform the development of more effective clinical trials going forward.

Concurrently, we need to develop more effective tools for molecular and systems approaches ranging from proactive health optimization and disease prevention to reactive ill health amelioration based on "-omics" haplotypes and novel biomarkers. Effective biomarkers are just one component of the solution. Though traditional biomarkers are

chemical in nature, alternative markers of increasing specificity, of cognitive and physical activities and abilities, could have broad implications for health care and wellness. Several preeminent programs at UC Davis, for example in nutrition and environmental toxicology could provide expertise for human phenotyping and genetic analysis as well as opportunities for genetics-based intervention strategies. The Foods for Health Initiative is a specific prospect for assimilation of human genetics components. The Biomedical Engineering faculty are leaders of in vivo phenotype imaging. By combining our growing knowledge regarding the role of specific genes and proteins in human health and disease with novel ways to target these entities in a manner that produces an externally detectable signal, it becomes increasingly possible to visualize and quantify specific biological processes in a non-invasive manner. Our Biomedical Engineering group has developed many new capabilities required for molecular imaging, particularly as applied to gene expression, and for high-speed and high-throughput screening. Molecular imaging techniques are ideally based on technologies that have an intrinsically high resolution (spatial and temporal) and allow the detection of low concentrations of target biomolecules (pico- to nano-molar range) such as nuclear imaging (PET, SPECT), nuclear magnetic resonance imaging (MR microscopy) or optical imaging. Appropriate funding will allow adequate curation capabilities and scaling of this technology. For example metabolomic biomarkers could be aligned with patient records for an additional dimension in point of care diagnostics. Omics data should be correlated with patient outcomes such as symptoms and health-related quality life which may promote new pathways for reducing burdens associated with chronic illness and enhance personalized health. There should be support to undertake proof of principle type studies in model systems for this translatable application.

Food, Feed, Feedstocks, Fuel, Fiber and the Environment

Desirable outcome: High yielding, affordable, high quality food, feed, fuel and fiber with minimum environmental impact, and physical and economic access to same.

In the vein of stewardship of the land, billionaire investor Jim Rogers has posited that the future is in agriculture. With the 7th billionth member of humanity having joined the planet, global food security is probably the single most important issue facing civilization and, by implication, the planet over the coming decades. Food and agricultural production systems must be significantly enhanced to respond to not just a burgeoning world population but a number of wide-ranging and far reaching transformations that include a changing climate, degradation of arable land, increasing international competition, globalization, and rising consumer demand for improved food quality, choice, safety, health enhancement, convenience and provenance. New and innovative techniques will be required to ensure an ample supply of healthy food despite competing interests and this can only be achieved by improving the effectiveness of all components of the US agriculture sector. Innovation is essential for sustaining and enhancing agricultural productivity and this involves new, science-based products and processes that contribute reliable methods to improve quality, productivity and environmental sustainability (Newell-McGloughlin 2011). Davis is well positioned to contribute innovative sustainable solutions to these real world issues. Translating this innovation into commercial products is a challenge though and unless effective translation systems

are put in place and barriers removed, the US is in danger of losing its competitive edge in this arena.

Newell-McGloughlin, M (2011). Prospects for Increased Food Production and Poverty Alleviation. In "Plant biotechnology 2011: Basic aspects and agricultural implications" Editors: Arie Altman, Paul Michael Hasegawa, Elsevier (In Press)

Systems Approach to Food, Feed, Fibre, Feedstocks and Fuels Production

To meet the world needs by 2030, it is estimated that 40% more food must be produced from less land and less inputs, using less water, less energy, less fertilizer and less chemical control. The physiological optimum using traditional breeding has already been maximized for many crops and animals. Using evolving systems tools such as marker assisted selection, TILLING, transgenics, phenotyping and other tools we can introgress desirable traits into adapted germplasm to select for higher production and bypass metabolic bottlenecks. However, it is essential to balance production and environmental factors with more efficient use of resources (more productivity from less input and optimized nutrient partitioning based on conditions and function of the crop), for example by improving phenotypes better adapted to changing stresses, both biotic (pests/disease) and abiotic, such as drought, heat, salinity, marginal soils, inadequate nutrients.

With abiotic stress there is a meta issue that overlays many of the individual efforts, and that is climate change. This poses a real challenge in terms of available agricultural land and fresh water use. Apart from the obvious effects of climate change, the decline of crop yields, ocean acidification, poor nutrition and abiotic stress, population displacement and threatened ecosystems must be considered. In addition there are also broader, more systemic effects of drought beyond food insecurity such as decreased household income, the loss of assets due to slaughter of livestock, health threats due to the lack of water for hygiene and household uses, environmental degradation, and less sustainable land management. In this context solutions must be developed to adapt crops to existing but also evolving conditions such as marginal soils or harsher conditions related to cold, heat, drought and salinity. In general we need more efficient use of water (one third of world population is subject to water scarcity with 70% of fresh water being used by agriculture). Over 25 million acres of arable land has been lost to salinity with over 40% no longer arable. More rational and targeted irrigation systems and improved modification of plant traits would be desirable (for example using super switches to turn on or fine tune multiple traits, Transcription factors, Zinc fingers, transcription activator-like effectors (TALES)). These novel factors enable efficient, programmable, and specific trait manipulation and represent powerful tools for genome editing in situ. UC Davis's work on optimizing phenotypes as the most successful events in the controlled environment of the greenhouse may not translate to field conditions. We need more effective use of fertilizers and plant nutrients tailored to the need of the plant and the location of planting, for example modified shade response to increase growth density.

Renewable Energy

Mechanisms need to be developed to exploit multipronged approaches to the future of energy and synthetic feedstocks as no one approach will suffice in reducing our carbon

footprint. "-omic" approaches can be taken to modify organisms and their subcellular components in such areas as alcohols, alkanes, algal diesel, photosynthesis, and tapping solar energy from photon capture. These approaches and enzymatic and bioprocessing steps need to be integrated with engineering and scalable processing systems to optimize production of biofuels and synthetic feedstocks. The production of biofeedstocks for these renewable fuels and synthetics must be compatible with food and feed production systems to ensure inequities do not arise in resource use. Biofeul crops should ideally be produced in areas where there is less productive land for feed production. Duel ["dual"?] cropping could also be considered. In addition to providing possible solutions, agriculture is also a major source of GHG emissions. It comprises 18-25% of total source but the ratios of GHG contributions are 14% CO_2, 48% methane and 52% NO -- the latter is 300 times greater than CO_2 as a cause of greenhouse effect. Research should focus on carbon soil sequestration and nitrogen use efficiency Funding/deregulation mechanisms and coordination across relevant agencies should be in place to streamline this process.

To achieve these production aims there needs to be put in place trans-agency coordinated support structures that facilitate integration of science. engineering and technology to enhance productivity. For example projects could focus on developing optimized GPS in no-till applications paired with optimized seeds with all the input attributes that will insure that each seed is customized for the exact location and conditions in which it is grown and with limited environmental impact. In addition to the obvious reduction in chemical controls and growth agents it could include such lateral approaches as for example introgressing the phytase enzyme which enables bioavailability of nutrients for livestock and limits environmental pollution from supplementing animal feed with phosphorous which is excreted into the environment. We also need the development of tools and systems to anticipate, assess and mitigate impacts.

Plant Microbiome

The human microbiome has generated a lot of interest but the plant microbiome has barely been considered – there is considerable potential for studying and optimizing the finally tuned choreography of symbiotes, commensals and pathogens that make plant growth possible/challenging and will allow us to develop intervention tools to optimize productivity and adaptability to changing conditions. In the larger context greater than half the biomass on Earth is made up of microorganisms including bacteria, archaea, protists, fungi, unicellular algae and viruses. They are the most abundant and diverse forms of life on our planet and are the chief engineers of the global carbon, nitrogen and phosphorus cycles yet we know less that 1% in any detail. Davis is developing the tools, algorithms, and modeling systems that will allow us to mine the incredible potential that exists in the microbial world. Multiagency funding programs especially across USDA, NSF, DOE could help with catalyzing work in this area in this area.

Improved Human Nutrition & Food Safety

Ideally food should not just be sufficient to meet basic nutrition needs but should be optimized from both a nutrition and functionality perspective to insure prevention of disease and optimization of health through a genomics understanding relationship between diet & health. Correlative research must be supported to establish parameters

for food functionality. Diet and nutritional status are among the most important modifiable determinants of human health but little of this has been objectively quantified using evidence-based research. For example it is well known that the nutritional value of food is influenced in part by a person's gut microbial community (microbiota) and its component genes (microbiome). Unraveling the interrelations among diet, the structure and operations of the gut microbiota, and nutrient and energy harvest is confounded by variations in human environmental exposures, microbial ecology, and genotype. Eating patterns are established at an early age and these patterns impact BMI and disease risks as an adult. Genetic, epigenetic and observational data suggest that early food regimes can affect later life health. There is also a clear dichotomy in demonstrated need between different regions and socioeconomic groups, the starkest being injudicious consumption in the developed world and under-nourishment in Less Developed Countries (LDCs). Both extremes suffer from forms of malnourishment, one through inadequate supply, the other, in many but not all instances, through inappropriate choices, the latter often influenced by economic considerations. Dramatic increases in the occurrence of obesity, cardiovascular disease, diabetes, cancer and related ailments in developed countries are in sharp contrast to chronic under- and genuine malnutrition in many LDCs. Both problems require a modified food supply, and the tools of biotechnology and genomics, while not the sole solution, do have a significant part to play (Newell-McGloughlin 2010).

While the correlative link between food and health, beyond meeting basic nutrition requirements, has only been unequivocally proven in a number of cases, a growing body of evidence indicates that food components can influence physiological processes at all stages of life. Nutrition intervention from a functionality perspective has a personal dimension. Parsing individual response is at least as complex a challenge as the task of increasing or decreasing the amount of a specific protein, fatty acid, or other component of the plant itself. There is also evidence that early food regimes can effect later life health, e.g. some children that survived famine conditions in certain regions of Africa grew into adults battling obesity and related problems, presumably due to the selective advantage of the thrifty gene in their early food-stressed environment becoming a hazard during more abundant times especially if later diets are calorie dense and nutrient poor.

Another area that has not been subject to rigorous scientific inquiry is energy balance as there are not very precise tools to access effects. New labeled biomarkers could help with such questions as how does satiety work. Can it be manipulated to enhance energy balance? What is the dose response relationship between degree of physical activity and weight loss in terms of efficacy? Under which conditions does energy compensation occur in response to perturbations in energy intake and energy output? What are the effects of reductions in different body fat depots? The physiological impact beyond burning calories is not well understood novel markers need to be developed.

Public- private funding of joint programs addressing the continuum from modified plants to human haplotyping should be facilitated to establish research initiatives around this focus area of functional foods so that we can select and optimize for peak performance. With advances in metabolomic, lipidomic and epigenomic tools and biomarkers we can develop systems to not just view health as absence from disease but rather to implement

regimes for optimization of quality of life over a lifetime. Some of the most powerful and predictive biomarkers and surrogate analysis systems for these types of assessment namely the fields of glycobiomics and lipidomics were advanced at UC Davis. As a corollary to this biomarkers that are indicative of predisposition to diet related disorders should perhaps be taken into consideration when formulating health insurance plans as the impact on healthcare of ill-advised dietary decisions are not inconsequential. At the very least they should provide guidance for consumers to optimize their health and minimize their requirements for medical intervention down the line which is far more cost effective not to mention a better quality of life choice for the individual. This type of approach would require interagency efforts especially between NSF, NIH and DARPA

Newell-McGloughlin, M. (2010). Modifying Agricultural Crops for Improved Nutrition. New Biotechnology. 27:5, 494-504

Epigenomics

Increasing our understanding of epigenetic patterns, their significance and role in development, evolution and adaptation and on small molecules (nutrients, drugs, toxins – therapeutic and food functionality applications) that reverse epigenetic activation/inactivation should provide us with the means to "unlock" silenced (enhanced) genes, (for example in nutritional epigenomics to "convert" the obsolete human thrifty genotype into a "squandering" phenotype).

Reduced waste throughout the supply chain

It is estimated that between 50-70% of produce is lost post-harvest. Areas that could be focused on to reduce this loss include the use of genetics/genomics to increase shelf life, modify cops to improve bioprocessing characteristics and processes and minimize waste in the food chain through the use for example of smart nanopackaging to detect/retard spoilage. Reducing incidences of food-borne disease. There is a false dichotomy between natural and manmade when the focus should be on science-based cost/benefit analysis. Some of the worst toxins in world are natural – for example mycotoxins are known health risks causing such problems as liver cancer to humans and animals. Bt corn results in a 90% reduction in mycotoxin fungal fumonisins. Pragmatism should prevail to insure safety Bt protection in cereal and cecropins to protect against bacterial contamination although none of those transgenic approaches have progressed beyond the greenhouse with the result that Washington state is forced to rely on sprayed antibiotics to combat fireblight infection rather than approve the more sustainable safer biotech approach (see disproportionate regulation barriers below)

Health Optimization

Below is an outline of some additional focus areas not well served by current funding sources and with the potential to be transformative within the Life Sciences interdisciplinary sphere. These examples represent major themes including broad scope technologies and important problems. They range from somewhat prescriptive to open-ended and are not meant to be exhaustive or comprehensively outlined but to be indicative of opportunities. Providing adequate support to facilitate translation of these fundamental sciences is crucial. Davis has a number of centers with a translational focus

including the Clinical and Translational Science Center (CTSC) which is a major local, regional and national resource that advances translational research over a wide spectrum. With strong infrastructure capabilities, visibility, as well as focus on training and team science and the potential to foster growth in novel areas, the CTSC offers a wealth of multidisciplinary interactions to support the bioeconomy.

Regenerated and Rejuvenated Replacement Parts

The assemblage of building blocks into complex functional structures has been a hallmark of nature and of engineering. As molecular, cellular, and tissue biology and engineering are increasingly mature fields and applied to medicine, the next scale of challenge is the organ, whether a heart, kidney, or knee joint. Just as chemistry and physics have catalyzed the assemblage of materials and circuits using mechanical, and electrical engineering approaches to create laptop PCs, biological building blocks can be turned into tissues and organs. Such organs could be regenerated within the body or incubated outside for subsequent implantation. At Davis during the last five years, considerable resources have been focused on developing regenerative medicine and stem cell research. The Institute for Regenerative Cures includes not just state of the art labs but also a Good Manufacturing Practice facility and the possibility of realtime imaging with an onsite radioisotope facility. These type of joined up research endeavors from discovery to clinical applications are difficult and costly to fund. Provisions should be created to support structures such as on-site partnerships between multiplexed industry collaborators.

Global pandemics

Infectious diseases are primarily a third world concern – Can we bring first world science to bear on elucidating targets and solutions? There is opportunity here for integrating multiple different dimensions of information that will be needed to solve this problem (pathogen-vector interactions, pathogen-host interaction, etc.) We must be prepared to anticipate zoonotic diseases, coming pandemics in plants, animal, humans. It is estimated that 70% of upcoming threats to humans are of zoonotic origin. The narrow genetic base of our crops and animals make them more susceptible to annihilation by virulent pathogens. We need to develop better mechanisms to anticipate and mitigate against coming pandemics. For example there could be a focus on the development of novel DNA/RNAi based diagnostics and beyond that antimicrobials that could evolve in response to the evolution of the pathogen and circumnavigate the issue of pathogen resistance.

Synthetic Life

Engineering novel metabolic pathways from microbes to higher organisms for application to the biomedical and environmental fields. Methods must be developed to deal with the intrinsic noise in the system and approaches that will provide a level of robustness to thrive. Many is this area are not going to succeed because they are failing completely to take into account the intrinsic noise structure in the systems that provided level of robustness to survive (so without this the system will quickly fall apart). This is a source of variation that is virtually ignored in the sciences.

From Apoptosis to Aging

Death is ubiquitous and the ultimate outcome of all things living, be they cells or organisms. While death usually has a negative connotation animals have learned to use death to their advantage, for example, to get rid of unwanted cells and to increase their evolutionary fitness. The extended survival of the individual at the expense of reproductive fitness in stressful environments be it bristle cone pines, dauer state worms or starving rats provides an intriguing insight into the balance of selection of the individual versus the group. (Is glucose the problem?) Can we, as individuals, tip that balance in our unit's favor?

On another level as we become more effective at this, balancing the need of the individual versus that of the group will become an issue as a growing aging population is supported by a disproportionately smaller productive working-age population. The healthcare system, welfare system and the environment are impacted by the drain on resources of non-productive individuals. Integrated living systems, extending the productivity of individuals and minimizing impact on the healthcare systems should be a priority.

The Mind: Know Thyself at the Molecular Level

Brian Greene, when asked what are the top three questions in science?: 1. the origin of the cosmos, 2. the origin of life, 3. how consciousness arises. While we have made inroads into many arena of enquiry the mind and consciousness remains a largely uncharted territory where science and the tools at our disposal are still at a primitive level in terms of technology and progress towards understanding. It provides a fascinating arena of study ranging from the mundane elucidation of the mechanism of disease cause and progression to the more esoteric notion of how and why we can ask those questions. Can multidisciplinary approaches help us to find answers to those questions and to unlock the mind's potential? At UC Davis the MIND Institute houses interdisciplinary and clinical/treatment research on human neurodevelopmental disorders while the Center for Neurosciences integrates faculty in a unique academic setting focused on basic and translational science that complements many of the more clinical efforts of the MIND Institute and the Neurotherapeutics Research Institute focuses on the development of targeted treatments for neurogenetic disorders. This type of interdisciplinarity can potentially provide us with a handle on the complexity of disorders that form the spectrum of autism syndromes.

(3) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative 1)?

Large data management

To us one of the greatest challenges that requires a platform solution is how to adequately curate, manage and mine the Tsunami of data that the tools of modern biology are generating in an ever growing surge. The massive volumes of data however is not just being generated from genomics research but across multiple technology platforms

(sequencing, genome-wide-studies, imaging, microarrays, proteomics, metabolomics, lipidomics, glycobiomics, tissue maps) and is now beyond the reach of most researchers, so that every day they make decisions on everything from experimental design to clinical trials based on inferior or incomplete information sets because they lack the ability to harness the power of the big data sets that inform their areas of interest. The ultimate goal of the field is to enable the discovery of new biological insights as well as to create a global perspective from which unifying principles in biology can be discerned. There are three important sub-disciplines within this so called life sciences informatics: the development of new algorithms and statistics with which to assess relationships among members of large data sets; the analysis and interpretation of various types of data across datasets including nucleotide and amino acid sequences, protein domains, and protein structures (the so called semantic web); and the development and implementation of tools that enable efficient access and management of different types of information stored in many types of formats (the meta web).

Davis has the expertise and capability to develop and apply the computational tools necessarily to address these challenges so that useful information can be extracted and converted into enabling technologies which can rapidly be reduced to practice and applied in everything from finding and introgressing novel traits in plants and animals to respond to changing stressors and optimize quality and productivity, to designing novel biomarkers for assessing individual response to, and anticipation of, nutritional and disease states. University- private sector collaborations are best served to deliver in this space. The Genome Center faculty provides numerous opportunities for multidisciplinary collaborative genome-scale research. The GC provides leadership through focus groups in epigenetics and networks biology, and, currently in protein-structure function and metagenomics. New scalable capabilities now provided by on site computational power of the Beijing Genome Institute.

(4**) The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes? Moving life sciences breakthroughs from lab to market: It is a challenge to commercialize advances in the life sciences because of the risk, expense, and need for many years of sustained investment. The Administration is interested in steps that it can take directly, but is also interested in encouraging experimentation with new private-sector-led models for funding commercialization of life sciences research.**

As Jim Gray (The Fourth Paradigm) noted we must do better at producing tools to support the whole research cycle – from data capture and data curation to data analysis and data visualization. Most areas of science, simulations and experiments are drowning in data, with some areas facing zettabytes of data in near term. This includes not only static, but also dynamic datasets (where data are continuously streamed and need to be analyzed in real time). This trend towards more data is likely to continue in the

foreseeable future. Everyone from the sciences to the humanities to citizens and representatives, face daunting problems in making use of this expanding digital resource. Our ability to manage, mine, analyze, and visualize the data is fundamental to the knowledge discovery process. The value of data at extreme scale can be fully realized only if we have end-to-end solutions, which demands collective, inter-disciplinary efforts to develop. This will require input and collaboration from a range of experts from computer science, engineering, bioengineering, and other domain scientists, data analytics experts and visualization researchers, users, designers and animators to foster common ground for solving problems that face us now and those that will face us in the years ahead.

The expertise, equipment and reagents need to achieve this at a level that can deliver commercial products is greater than any individual institution can achieve. Mechanisms should be put in place to support large scale multi institutional efforts that will allow sharing of resources from human capital to high end equipment for example allowing the paring of national labs with public and private sector institutions and reconsidering the restrictive working environment and overhead requirements of the former. Novel funding structures should be created for the democratization of open source and distributed systems such as cloud computing and the semantic web. Other mechanisms are outlined above and under question 17.

(5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

The principal barrier is funding the gap between precompetitive research and a commercializable product. Funding mechanisms should be put in place to bridge the valley of death that currently falls between the remit of both ends of the spectrum. The work that is too far downstream to be considered discovery yet too far upstream to be considered truly pre-commercial, often falls between the cracks. Additional issues are regulatory and IP restrictions. Beyond regulatory burdens (covered below) how can the public agricultural research sector implement a paradigm of translational research? As noted by Bennett (2010) mechanisms should be put in place to facilitate researchers in agricultural biotechnology to anticipate the downstream development, deployment, and commercialization requirements from the outset rather than trying to figure out process after the fact. Funding mechanisms should be in place to help with the costly compliance with regulatory requirements and intellectual property access, and to allow investigators to determine how to bring the project results to scale. To achieve both basic research goals and successful translation, research teams should include members from multiple disciplines (including legal and policy experts) and maintain a high degree of connectivity and communication. Translational research must be characterized by clear accountability focused on progress toward deliverables.

If the public sector is going to contribute in tangible ways to meet this vision of the future of the bioeconomy, the public research system needs to be optimized for translation in

this arena. An additional impediment that public sector researchers often encounter is that the constructs for which they have FTOs in research applications are patent-protected and must be licensed at some cost before a product can be considered for commercialization. Bench marking standards and best of breed should be created facilitate this type of translation. At Davis we have created the Public-Sector Intellectual Property Resource for Agriculture (PIPRA) which seeks to assist both public and private sector crop developers to assess the IP terrain, to develop licensing and other types of agreements, and to formulate a commercialization or product release strategy.

Bennett, AB (2010) Food Security: Translational Agriculture, Science 23 April 2010: 429.

(6**) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs 2 would help accelerate commercialization of federally-funded bioeconomy-related research?**

Make the funding more flexible by extending the definition of SBIR/STTR to include nontraditional enterprises. Increase the first tranche to allow more work on precompetitive research and proof of principle applications. Small business catalytic grants should be created to accelerate this process.

(7) What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

The government has many valuable datasets such as outcomes of clinical trials negative and positive, disease distribution statistics that may correlate with regional/socioeconomic effects such as for example obesity, T2DM that may inform the development of biological intervention regimens and/or therapeutic solutions. Making those accessible and searchable (while obviously insuring that they comply with GINA requirements) could help with recognizing and developing research initiatives.

(8) **What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?**

Current funding models are too limited and restrictive. There is funding for basic discovery research and for <u>downstream</u> products but little to fund the chasm between. Proportional buy in and equity ownership needs to be revisited. Funding structures should be established to support entrepreneurial startups that need scalable investment options with the appropriate balance for risk tolerance.

Workforce development: Investment in education and training is essential to creating a technically-skilled 21st century American bioeconomy workforce.

(9) T**he majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?**

A recent report from the Commission on the Future of Graduate Education opined that innovative solutions to many of the challenges facing the United States and the world in the 21st century will depend upon a creative, knowledgeable, and highly skilled workforce. They note that graduate education is the system that provides students with the advanced knowledge and skills that will secure our future intellectual and economic leadership in the knowledge economy. At Davis we have a number of innovative training programs that provide well-coordinated, cross-disciplinary training of graduate students in critical areas of technology research and promote interdisciplinary research environments that integrate basic biological and physical science, engineering and computational disciplines. We emphasize that we are not training generalists. Our philosophy is that successful interdisciplinary interaction is rooted in scientists who have an in-depth command of their discipline. In addition they must have the facility and drive to reach out across disciplines to forge new fields and to integrate research approaches to solve problems in fundamental and applied science. It is this qualitative interdisciplinary training that our programs provide in addition to the rigorous comprehensive discipline-oriented training of the graduate groups. Likewise, creating a nurturing environment for entrepreneurs should be a priority for research institutions with courses, internships, public-private mentors, job shadowing and opportunities to spin off companies as part of the graduate trainee experience. These should have, at a minimum, required internships and industrial advisory committees but courses taught by private sector instructors or guest lecturers would be even more effective.

(10) What roles should community colleges play in training the bioeconomy workforce of the future? Community colleges are crucial for training the technical workforce. If sufficiently resourced they can provide the human capital that especially will help with the scale up requirements of the biotech industry. Funding mechanisms to facilitate collaborative grants with four years institutions and retraining programs could help to fill this pipeline.

(11) **What role should the private sector play in training future bioeconomy scientists and engineers?**

An integral aspect of our training programs is cross-disciplinary training in company laboratories and enhanced modes of scientific communication and exchange with industrial affiliates. This industrial experience provides mid-career students with an industrial view of how research is accomplished, stimulates interaction between campus and industrial scientists, and helps make known to the general scientific community tools, technologies and protocols that are available in both sectors. It also enhances the entrepreneurial atmosphere on campus by providing a forum for industry interactions. Other novel aspects include flexible instruction in methods and techniques and the participation of company representatives in activities such as seminars, retreats, curriculum development and teaching. The two-way communication fosters increased connectivity of campus research to the process of commercialization. Biomedical research workforce development requires new approaches because of today's increasingly complex scientific and technically sophisticated knowledge base, which includes multiple fields from bioinformatics, statistics, genomics, nanotechnology, bioengineering and

regenerative biology. Industry can help provide access to the cutting edge techniques and instrumentation that may not be readily available on academic campuses

(12) **What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?**

The research workforce must evolve with our rapidly changing scientific development - Trainees require a new set of core knowledge competencies in addition to the traditional scientific disciplines so that they can optimize their potential to make translatable discoveries. Funding should be made available to support even broader interdisciplinary training to expose life sciences researchers to facilitating interaction between departments with complementary expertise for startups; for example, partnering with business students to help with business plans, engineering students to help with product design and testing, and law students to resolve IP and other legal issues. Leadership training consortia should be supported to facilitate multi-institutional team applications to corporate sources of graduate training support. For example the federal and state governments could create mechanisms to incentivize corporate financial support of graduate training activities. The idea of providing tax relief similar to that awarded for corporate investment in research may be an appropriate approach by legislators. Currently, at UC Davis corporations invest in specific-interest projects; however, to achieve a sustainable funding system, broad based matching traineeships should be created through leadership training consortia to liaise with industry and establish long term training partnerships.

Reducing regulatory barriers to the bioeconomy: As President Obama has stated, our regulatory system must ''identify and use the best, most innovative, and least burdensome tools for achieving regulatory ends'' and ''protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation.''

(13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

Over the past 20 years, private companies have only invested in the development of a few traits in a few major crops. As a result, specialty crops and traits with high environmental, social and regional value are being overlooked because the barriers to entry are considered too prohibitive. McDougall (2011) suggests that it now takes $134 million and almost 14 years to get an ag biotech crop to market. Universities and other public sector research organizations that have traditionally produced new varieties of such crops are poorly prepared, both financially and technically, to commercialize GE crops, and few have been successful. Despite more than two decades of public research investment, only two GM crops developed in the public research sector have been approved for commercial release. One of those, the papaya resistant to ringspot virus single handedly saved the papaya economy in Hawaii including the organic market as it significantly reduced the viral reservoir. Likewise, for some significant commodities with narrow genetic bases, such as citrus and grapevines, there is an ever-present risk of their being

decimated by pathogens and little traditional methods for insuring sustainable resistance. We are in danger of losing those industries permanently if a more rational regulatory oversight regimen is not instituted. The director of regulation for a large multinational seed company has noted that if the cost for regulatory approvals was significantly less, his company would likely have moved forward with over ten important products with useful traits. But when they did an NPV [net present value] analysis with the major cost being regulatory they ended up cancelling each and every one because the NPVs were too low. While consumer rejection is frequently cited as a factor discouraging the development of GE specialty crops, the results of a number of surveys suggest that if GE foods offered health or taste advantages, consumers would buy them, even at premium prices (Rommens, 2010). Thus it is increasingly clear that the major bottleneck in bringing quality-enhanced GE specialty crops to consumers lies in the cost and complexity of the regulatory process.

A 2004 NRC study reaffirmed that there was no scientific justification for singling out rDNA techniques as more risky than other plant genetic modification techniques now regarded as conventional, including tissue culture, chemical and radiation mutagenesis, wide crosses, embryo rescue and polyploidization. In 2010, the European Commission published a summary of the past decade of EC-sponsored research in the European Union on the safety of genetically engineered organisms which followed on its 2001 document summarizing the first 15 years of such research. It states: "The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not per se more risky than e.g. conventional plant breeding technologies." The European Union has spent more than EUR 300 million on GE biosafety research since 1982.

And transgenic animals take this irrationality to another level since GE food animals are regulated as drugs based on the notion that a transgene meets the requirement of "articles (other than food) intended to affect the structure or any function of the body of man or other animals" blithely ignoring the fact the all forms of traditional breeding could be captured by a similar stretch of the definition! As such they must go through the USFDA new animal drug approval process. This means that products must be proven to be safe and effective as well as provide an assessment of its environmental impacts, under the requirements of the National Environmental Policy Act (NEPA). As Van Eeneenam and Muir (2011) note, similar to the situation with plants, subjecting conventionally bred and GE animals to different regulatory standards is inconsistent from a scientific perspective and places an excessive regulatory burden on the development of GE technologies. They add that assessing potential risks in the absence of considering concomitant benefits and those risks associated with alternative food production systems gives disproportionate emphasis to the risk side of the GE food animal equation. Few, if any technologies could survive a risk-only analysis. Specifically with respect to the GE salmon they note that wild-caught fish deplete the oceanic stocks and do not present a long-term, ecologically sustainable solution to rising global fish demand. One of the benefits associated with the development of GE fish for aquaculture may well be in helping to reduce recognized pressure on wild fish populations as we threaten to deplete our marine resources.

Alison L Van Eenennaam & William M Muir (2011) Transgenic salmon: a final leap to the grocery shelf? Nature Biotechnology 29, 706–710

McDougall (2011) The cost and time involved in the discovery, development and authorisation of a new plant biotechnology derived trait A Consultancy Study for Crop Life International

Rommens CM (2010). Barriers and paths to market for genetically engineered crops. Plant Biotechnol J 8: 101-111.

(14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

Fedoroff et al (2010) rightfully propose a rethinking of the regulatory system to support public-sector development of ag biotech in the United States and as an international precedent. As noted by Bennett (2010) this strategy will only be effective if it is coupled with a comprehensive translational research paradigm for public agricultural research—analogous to the approach that the National Institutes of Health has been adopting since 2003 to better link basic research to patient needs.

Regulations must be rationalized to be proportional to the actual risk involved. The most that can be expected of any oversight regimen is that products developed using all methods should receive the same level of evaluation both with regard to impact on the environment and safety to the consumer. Millions of people have already eaten the products of genetic engineering and no adverse effects have been demonstrated due to the techniques per se. Both current science and long-term experience support the repeated conclusions of learned bodies that it should be the product, not the process by which it is developed, which should be evaluated for both risk and benefit.

The FDA remains the most rational of the agencies when it comes to appropriate regulatory focus in so far as plants are concerned but for animal all agencies are equally culpable. USDA APHIS and the EPA are the prime agencies whose approach states that the focus is on the product yet clearly it is the process (and not the product) that results in triggering oversight assessment. This must be ultimately changed to insure the proper checks and balances are in place. Scientists are confident that if we do not focus on the scientific method in judging the safety of the food supply and the impact on the environment, we will slow or destroy the advances that will reduce the use of unsafe chemicals and less safe agricultural practices in this country and we will limit the potential of novel products, improved productivity, nutrition and quality that promise to strengthen the agriculture economies in the US. With due consideration for public and environmental safety, the arbiter of product value should be the marketplace not the regulatory agencies. Otherwise innovation will be stifled and the US will lose its supremacy.

Fedoroff et al (2010) Radically Rethinking Agriculture for the 21st Century

Science 833-834.

Bennett, AB (2010) Food Security: Translational Agriculture, Science 23 April 2010: 429.

(15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

The costs of regulatory oversight need to be rationalized and the focus needs to be on risk assessment based on the product not the process by which it was produced. The fact the Geron has abandoned its promising stem cell clinical trial is indicative of the out of control costs of clinical trials. It is estimated that it now takes approximately $1B and 13/15 years to get a product through trials to market. This type of cost is not sustainable going forward. The EU Medicine Authority (EMEA) approved the first recombinant therapeutic from an animal bioreactor (ATryn, an anti-clotting agency expressed in the mammary gland of a goat) two years before the USFDA had even formulated its policy for oversight of animal-based pharming.

Likewise the majority of therapeutics are designed to target single proteins/receptors. The FDA clinical trial process is designed to test single drug effects and has no capacity for testing the more effective multiple interaction synergistic approach to therapeutic development which promises to be the most effective medicine of the future as we move towards a metagenomic view of drug metabolism. Developing more effective modeling systems such as for example topology of protein-protein interaction networks, it is possible to develop methods that can explicitly model the possible synergistic effect of targeting multiple proteins using drug combinations in different disease such as cancer types. This could inform the development of more effective clinical trials going forward. Development of surrogate preclinical testing systems such as differentiated stem cells could also help with shortening the clinical trial process and accelerating commercialization.

On another level commercialization of the products of recombinant DNA technology is just another facet in a long history of human intervention in nature and as such the same parameters of risk-based assessment should apply. It must be undertaken within a regulatory framework that ensures adequate protection of the consumer and the environment while not stymieing innovation that may result in beneficial consequences. The science of biotechnology offers efficient and cost-effective means to produce a diverse array of novel, value-added products. If regulatory burdens are disproportionate we will end up relying on older less effective less sustainable and less competitive processes and products which will inevitably have a negative impact on the bioeconomy.

Public-private partnerships: The Administration is interested in serving as a catalyst for public-private partnerships that build the bioeconomy and address important unmet needs in areas such as health, energy, agriculture, and environment.

(16) What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

The highest impact is partnerships for pre- competitive research with shared interest and willingness to share best practices, equipment and expertise to achieve a common goal. Stakeholders would include universities private research institutions, industry and philanthropic organizations. For example UC Davis and Lawrence Livermore have a joint Bio and Medical Technology Development Industrial Partners Consortium. By working together, Livermore, the UC Davis Health System, and industrial partners form a complete "laboratory bench-to-bedside" cycle for innovative medical technologies. Livermore's Medical Technology Program and Biology and Biotechnology Research Program and the UC Davis Health System are experienced in identifying critical medical needs, researching new concepts, and developing prototype devices. This will enable the industrial partners to develop these devices into commercial products, shepherd them through the approval process, and distribute them to the medical profession.

(17) What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for precompetitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

There are many mechanisms to optimize public-private interactions from precompetitive open innovation support, to straight licensing. But in most instances, for public institutions, nurturing long term collaborations with the private sector is often a more sustainable option. Open innovation hubs that encourage investment from multiple sectors and stakeholders should be encouraged with seed funding at research institutions whose principal remit is discovery research to encourage them to take risks on more mission oriented research. The garage concept of QB3 within the UC system and the Broad institute are examples where this type of stakeholder involvement from the basic to the most mission oriented research is nurtured. Standford Innovation Corps (I-Corps) focuses on scientists and engineers whose academic research has business potential but needs development. UC Davis is also initiating the Research Investment in Science and Engineering (RISE) program which is designed to facilitate the clustering of outstanding researchers in highly competitive teams to exploit opportunities in science and engineering where the complexity of the research agenda requires the advantages of synergy, scale and shared resources that clusters of research partners can provide. This approach will allow teams to carry out joint research activities in areas of strategic importance, while also giving the time and resources to generate data to attract and cultivate strong external partnerships that can facilitate the translation of this research into commercial products.

Too much research investment is not capitalized upon and exciting IP is not captured as the universities and research institutes do not have the resources or personnel to work at

this interface. Funding mechanisms should be created to resource the institutes to allow effective translation and optimize transfer of technology to the private sector. It is essential that experts from the private sector are part of this process and they have the expertise, experience and perspective that may be lacking in those with a purely academic background.

Innovation type hubs should be supported that will better connect campus research with entrepreneurs and accelerate the transformation of university inventions into commercial products and services. The creation of ecosystems that fosters technology transfer and build long-term relationships among the campus, industry, local governments and communities would hasten "deal flow" through the system and a more rapid road to commercialization. Support should be allocated to incentivize these type of interdisciplinary problem-focused collaborative environment that spurs innovations in learning and research by discovering ideas that take shape at the frontiers and intersections of academic disciplines. Funding should be focused on a range of incentives and funding mechanisms, training programs, policies, reward structures and recognition opportunities for faculty, staff, students, and external partners that foster innovative collaborations, self-sustaining initiatives, team science, "high-risk/high-impact" discovery, next-generation technologies, entrepreneurial activity and other forms of core, interdisciplinary translatable enterprise.

Likewise, creating a nurturing environment for entrepreneurs should be a priority for research institutions with courses, internships, public-private mentors, job shadowing and opportunities to spin off companies as part of the graduate trainee experience. These should have, at a minimum, industrial advisory committees but courses taught by private sector instructors or guest lecturers would be even more effective.

The UC Davis Child Family Institute for Innovation and Entrepreneurship builds on the success and experience of the UC Davis Center for Entrepreneurship, which since 2006 has helped researchers and students move their innovations and ideas into the marketplace. The institute will help to integrate innovative and entrepreneurial thinking and actions across the university, and strengthen UC Davis' role as a vital player in catalyzing economic development in the region, state and beyond.

The principal barriers to effective partnerships are navigating the IP landscape and effectively optimizing ROI for all partners. Clear goals, expectations and division of labour must be established *a priori* to mitigate against any unanticipated obstacles to success developing down the line.

STATE OF ARKANSAS
MIKE BEEBE
GOVERNOR

December 5, 2011

Dr. John P. Holdren, Director
Office of Science and Technology Policy
Executive Offices of the President
725 17th Street, Room 5228
Washington, DC 20502

Dear Dr. Holdren:

The State of Arkansas, along with the United States Food and Drug Administration (FDA), has recently undertaken a bold initiative to meet the "grand challenges", as set forth in the Request for Information on Building a 21st Century Bioeconomy, by partnering to create the Center for Excellence for Regulatory Sciences. I offer my support for the attached responses from the FDA's National Center for Toxicological Research (NCTR) to the Request. I am confident that this partnership is an important component in helping the Office of Science and Technology Policy (OSTP) develop a successful National Bioeconomy Blueprint.

I am convinced that the work being accomplished by the professionals at the NCTR is critical to meeting the national objective of creating a strong 21st Century Bioeconomy. The expanded sharing of resources, facilities, and education initiatives supports the goal of utilizing the embedded resources in Arkansas to meet the opportunities of the emerging bioeconomy.

As stated in the Request, biological research underpins the foundation of a significant portion of our economy. I look forward to strengthening the partnership with the federal government through this important economic development initiative.

Sincerely,

Mike Beebe

MB:jb
Enclosure

UALR

OFFICE OF THE SPECIAL ADVISOR TO THE
CHANCELLOR FOR ECONOMIC DEVELOPMENT

December 6, 2011

The Honorable Dr. John P. Holdren,
Director of the Office of Science and Technology Policy
Executive Office of the President
725 17th Street, Room 5228
Washington, DC 20502

Dear Dr. Holdren:

I am pleased to submit a reply to the Request for Information on Building a 21st Century Bioeconomy. Arkansas Governor Mike Beebe has asked me to take a leadership role in this activity, a task which I have eagerly accepted. I am excited about our activities in Arkansas, especially those that work to collaborate with and extend the effectiveness of FDA's National Center for Toxicological Research. I have worked with NCTR for years and have the highest regard for its scientific excellence and its vision for improving public health through collaboration with academia and industry. Those of us in academia have enjoyed their collaboration and have utilized the excellent staff in teaching and research collaborations.

I believe we have a set of suggestions that can have a profound effect on speeding commercialization within the bioeconomy. As Co-chair of our Center of Excellence in Regulatory Science, I will look forward to more discussion and exciting new interactions.

Sincerely,

Mary L. Good

Mary L. Good

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AN ARKANSAS RESPONSE
To A Request for Information from OSTP
Building A 21st Century Bioeconomy

Introductory Statement:

There is one major impediment to harnessing biological research innovations for the bioeconomy. Research resources have not been directed to the science of rapidly assessing the toxicity of those innovations. Cutting edge research leading to product development is essential but not sufficient. We also need cutting edge research into understanding potential toxicity early in the development process. Without that capability, product approvals are lengthy, expensive, animal-intensive and the cause of enormous levels of uncertainty. Uncertainty leads to lack of investment and lack of commercialization.

Arkansas is home to the one facility dedicated to that mission, the internationally acclaimed[1] National Center for Toxicological Research (NCTR)[2]. Properly funding the practical research at NCTR would have a very large, positive impact on the bioeconomy, especially in the biomedical, food, cosmetic, and veterinary product areas.

Arkansas has taken a strong step to contribute its resources to the resolution of this problem. Arkansas has entered into a Memorandum of Understanding[3] and a subordinate Collaborative Supplemental Agreement[4] with the Food and Drug Administration. The agreement establishes a Center of Excellence in Regulatory Science that will focus on research in the area of nanotechnology, especially developing rapid indicators of toxicity; doing so in collaboration with industry, academia, government and public partners; establishing data mining techniques utilizing the latest information technology; providing certificate- and masters level training courses; analyzing policies and procedures leading to commercialization; aiding commercialization through providing business advice and suggesting funding sources; and an accountability/review process with FDA and others. A Working group consisting of representatives from federal and state government, academia, industry and the public has been established to coordinate the activities of the Center of Excellence.

(1) *Identify one or more 'grand challenges' for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.*

The "grand challenge" Arkansas wishes to address includes experimentation, novel ideas, improving the regulatory process, consideration of research priorities, use of public-private partnerships, reduction of barriers to commercialization, workforce development, technology transfer and more.

- It understands the critical importance of the practical research conducted at NCTR and supports it in a program that combines Arkansas assets with those of NCTR; focuses them on one component of the bioeconomy, *i.e.,* understanding and providing the tools to rapidly and accurately detect the toxicity of products derived from nanotechnology; instructing participants regarding the regulatory processes; speeding commercialization; improving decision-making; and doing so in a collaborative effort with government, academia and industry.
- It establishes a collaborative effort between Arkansas's medical research facilities at the University of Arkansas for Medical Sciences (UAMS) along with other Arkansas research universities, state government, NCTR, the Food and Drug Administration, private industry, organizations whose purpose is to help emerging technologies become successfully commercialized and a major volunteer effort devoted to improving the regulatory science base and enhancing commercialization in this area related to nanotechnology.

- It continues—and increases—support for research leading to new therapies, diagnostics, cosmetics, food and agriculturally related products and others derived from nanotechnology, incorporates and supports the co-participation by NCTR to provide safety assessments, incorporates private industry into a draft standards-setting process and data sharing, creates masters-level and certificate-granting courses in Regulatory Science, incorporates the science of data reduction and computer modeling to provide more access to- and validation of- data from diverse sources, and develops proposals for concurrent scientific peer review to assure the highest level of scientific assessment.
- It recognizes global development of products using nanotechnology, but nowhere else is there the collection of resources like those in Arkansas to assess their safety. NCTR has a unique nanotoxicology capability with world-class expertise. NCTR has the decades of experience required to conduct safety studies using an internationally recognized "gold-standard," one that very few are capable of meeting. When combined with the drug, diagnostic and other product development in our academic institutions, we have the opportunity to pull resources together in a unique manner and to work within this defined area, nanotoxicology.
- It understands that the proof of value for this experiment will be its practical, measurable impact on facilitated commercialization of safe and effective products. Accordingly, it focuses heavily on detection of barriers to this process. Barriers, whether technical, policy, social or other will be identified, proposals for improvement will be developed, and meetings will be held with regulatory policy-makers to refine and implement recommendations. The transparency of this process will provide the means to measure success and accountability.
- It is intended in part, to test the premise that since old models of regulatory approval are proving inadequate for today's global technology and markets, new models are possible in which the regulatory agencies work cooperatively with industry, academia and the scientific community. Our desire is to create such a model in Arkansas and offer successful components to other regulatory agencies and a broader line of technologies.
- It mobilizes the private sector's abilities in business planning, capital formation, business management to work with the academic and government laboratories to reduce barriers to commercialization.
- It invites the participation of other federal agencies into this process, including those from Commerce, Defense, NIH, USDA, EPA, and others to join in with FDA and Arkansas to create a council for barrier reduction.

RESEARCH AND DEVELOPMENT:

(2) What should be the Federal funding priorities in research, technologies, and infrastructure to provide the bioeconomy?

- We need a re-direction of some research into predicting safety. This research is applicable across products and is beyond the ability of industry to conduct. When government is not doing enough, the consequences are delayed product approval.
- Providing adequate funding for NCTR is the most important step for the U.S. to be successful in the bioeconomy. NCTR helps develop the latest technology and applies it to predicting harmful effects. It develops tools such as those looking for early predictors of harm in saliva, blood, and urine; understanding the ways in which genetic variations affect metabolism and toxicity; understanding the relationship between nutritional status and harmful reactions; understanding the effect of variations (based on diet and geography) in intestinal microflora on drug metabolism; developing rapid (less than an hour) means of identifying micro-organisms; developing computer models; extrapolating results from animals to humans; refining models of risk assessment; etc.

- Within that need is recognition of the enormous impact on the bioeconomy of nanotechnology. Medical diagnosis and treatment, food production and packaging, cosmetics, manufacturing processes, and interactions with daily life we have not yet recognized will be dramatically different in the future. A review of the proportion of research funds devoted to nanotechnology devoted to safety assessment is an indication of the larger need for re-direction of research funds.
- Without a vastly different research focus, current regulatory capabilities and procedures will impose a barrier to the capabilities of nanotechnology and delay implementation at a huge impact on the bioeconomy, delaying cost-lowering diagnostic and therapeutic agents and adding to the existing high levels of uncertainty.
- The tools needed to assess the toxicity of nanomaterials are sophisticated and rare. NCTR has an excellent nanotoxicology facility, but its excellence is only relative to what is available elsewhere. More is needed to be responsive to the pull of the bioeconomy. More importantly, more scientists are needed. Exciting new drugs and cancer detection models based on nanotechnology are being developed in Arkansas academic facilities and elsewhere, but the current NCTR resource levels do not allow them to perform the needed assessments of toxicity. The need is magnified by the national scope of the NCTR task.

(3)(a) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research?

- Nanotechnology presents new challenges in toxicity assessment.
  - Traditionally, chemical structure has been the primary determinant in this assessment process. With nanoparticles, one must consider a host of other attributes including particle size, particle charge, shape, purity (much more difficult at the nanoscale), agglomeration, surface area and much more.
  - Understanding the chemical, physical and biological aspects of these particles is essential in determining impact within the body, dissemination and the multiple sites that may be affected, biological activity, metabolic properties, excretion patterns, effects on excretory processes and environmental impact.
  - Manufacturing processes must be understood in order to determine purity and variability.
  - The laboratory equipment necessary is both highly sophisticated and requires unique capabilities.
  - Facilities to house equipment such as electron microscopes with added spectrometers and other detection devices must be specialized to eliminate vibrations and control other conditions.
  - Expertise in this area requires specialized training and is not widely available.
  - The work requires some work with animals in facilities certified to provide only first-class animal care along with tightly controlled and measured diets and environments.
- Scientific papers and the press often report on small studies with apparent alarming results. The public sometimes has difficulty understanding that it takes huge studies with statistical power and years of experience and qualifications to conduct the level of study required to make responsible regulatory decisions. Many of these "alarming" results are found not to pose a human hazard, but only after damage may have been done to an industry. NCTR has the very rare capability to make these determinations properly. There is also a sophisticated, multi-layered, scientific review structure in place to provide external analysis of results. It would be inefficient to duplicate this capability elsewhere.

(b) What specific research priorities could address those challenges?

- The needed research encompasses more than the understanding of nanomaterials. It also includes bioinformatics, biostatistics, predictive computer modeling and others. All of these disciplines are housed at NCTR, but their utility could be much more powerful if funded adequately. (This

Arkansas effort will combine these capabilities in our universities with that of NCTR to accomplish more than is now possible.)

(c) Are there particular goals that the research community and industry could rally behind?

- Industry is certainly interested in innovative tools to predict toxicity early in the product development process and later during the variable conditions of use, *e.g.,* physical and metabolic interactions, multiple genetic variations, etc. Currently, these tools are evolving too slowly to quickly cull out "bad actors" during development, cut development costs, provide sufficient certainty in knowing whether products may be approved, and reducing the time required for approval and tests to be submitted for approval. These factors are major for the venture capital community. The lack of predictive tools can also lead to more concern that patients may be harmed which also adds massive liability concerns. Without these tools, consumers and businesses are both at risk to unproven claims of risk based on small, poorly designed tests, leading to fear and commercial impact when it may not be justified. Business and consumers need reliance on solid, proven methods to detect potential harm.
- If we are able to show positive impact, industry may want to help exploit available technology to mine data from all sources, public and private. In nanotechnology, we cannot afford the situation we have in other areas where massive amounts of data relevant to determining toxicity are unavailable for use. With new imaging and other technologies, standardized approaches to collecting and arraying massive amounts of data could be developed in a manner similar to the NCTR-developed ArrayTrack™ – a DNA microarray data management, mining, analysis, and interpretation software tool.
- Similarly, we believe there may be opportunities with closing of military bases and other areas to collaborate in developing a much more robust super-computing capability that could use existing expertise in modeling complex data to develop more predictive models.
- There is an opportunity to experiment with a process of sharing concerns and needs between researchers and industry, an effort that could impact some research agendas and lead to research efficiency and efficiencies in the development of regulatory standards.
- Creating a cadre of trained professionals who understand the intricacies of regulatory science could also be a common goal. This would seem to be even more attractive to industry if the training brings current issues to the discussion with a procedure to raise those issues to the level of regulatory consideration.

(4)What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

- Understanding the protein-coding function for genes is an intricate part of the NCTR work since it is so critical to understanding individual reactions to drugs. As more therapies are being personalized for individual genetic characteristics, this area is of increasing importance. This will be true for those therapies based in nanotechnology as well as others. This work is also receiving strong emphasis at our medical school (UAMS) as well as other Arkansas universities, thus funding the NCTR effort to develop safety procedures would serve as a multi-disciplinary effort through our Center of Excellence.

<u>MOVING LIFE SCIENCES BREAKTHROUGHS FROM LAB TO MARKET</u>:

(5) What can be done in the way of encouraging experimentation with new private-sector-led models for funding commercialization of life sciences research?

(a) What barriers are preventing biological research discoveries from moving from the lab to commercial markets?

- By far, the primary barrier is uncertainty in detecting down-stream toxicity and uncertainty in knowing if a product is approvable.

There are other barriers that could be addressed:

- Traditional granting procedures are a significant barrier to this work for Arkansas institutions. As the academic work proceeds, there is a need to engage the NCTR component to define the limits of toxicity. As HHS employees, NCTR employees may not be paid on NIH grants. Because the NCTR is underfunded, it often cannot provide resources to participate in this important work with our universities. If they were allowed to be funded on the grants, the hiring of postdocs, technicians and other staff would enable a huge amount of important work that simply cannot be accomplished under the present set of rules. The rules do not allow funding that would speed safety assessment and thus needed products are left undeveloped.
- NCTR has had many successful Cooperative Research and Development Agreements (CRADAs) with industry partners. Perhaps there could be a study of whether regulatory agency restrictions in those CRADAs should apply to NCTR since it has no regulatory responsibility.

(b) What specific steps can Federal agencies take to address these shortcomings (in academic labs, government labs or both)?

- Re-envisioning and re-positioning NCTR to be a facility where industry, academia and government come together to apply the latest technology to develop innovative, predictive procedures is the most important thing that could be done.
    - This recommendation was made previously by a Subcommittee of the FDA Science Board in November, 2007[5]. The report argues the FDA cannot fulfill its mission due to an eroded scientific base. It recommended the establishment of the type of facility we are recommending for NCTR. Also, The Subcommittee chair recommended that NCTR be considered for this designation[6].
    - The fact that NCTR it has no regulatory responsibilities and has worked collaboratively with numerous agencies and firms including Pfizer, AstrZeneca, Litmus, Sigma Tau Research, RxGen and others is important to this decision.

With respect to other steps:

- Perhaps OSTP could study this specific situation to look at options for resolution such as: when a grant application is successful and includes NCTR collaborators, a separate funding for the NCTR portion could be provided through an interagency agreement; or a separate funding track that rewards an NCTR researcher for a program with commercialization potential;
- Review and alter policies that fail to encourage collaboration between government, academia and industry. Legitimate industry knows that regulatory protection is essential to protect against fraud and to provide standards every manufacturer must meet. At least for the purposes of this Arkansas Center of Excellence, let us consider approaches that open some doors in the wall between the regulator and the regulated. Help us find ways to provide transparency, proprietary protection, and the highest quality scientific review.

(6) What changes to Federal Small Business Innovation Research and Small Business Technology Transfer programs would help accelerate commercialization of federally-funded bioeconomy-related research?

- Agencies could contribute representatives to work proactively with participants to become more deeply involved in the day-to-day process. The effort could become a program in which all federal agencies impacting this area of technology in this region could unite behind one comprehensive federal government presence, all devoted to adding to the experiment, focusing on problem-solving and barrier reduction in all of the areas covered by this Request for Information.

- Technology Transfer has too often become a slow, burdensome process. The Arkansas group plans to work with NCTR to remove barriers to more rapid implementation of technology transfer provisions. The intention is to facilitate the process while reducing the burden on both the laboratory (NCTR) and those seeking to transfer the technology. It would be more effective if a federal representative were to be an active participant.
- Since NCTR has no regulatory responsibilities, it seems prudent to review the policies and procedures that restrict NCTR compared to NIST and other facilities.
- The Arkansas Research Alliance, with a Board consisting of the chancellors of Arkansas's five research universities and top management from 16 major Arkansas corporations, with support from the Winthrop Rockefeller Institute, the Walton Family Foundation, instituted research conferences based on promising research focus areas. These conferences connect researchers and business leaders for three day conferences. Perhaps Small Business and Technology Transfer programs could offer assistance to ARA in this or similar programs and to participants in these programs. It may also be possible to extend their reach by bringing some of the excitement from technologies discussed at these conferences to students in order to stimulate interest.

(7) What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

- Much more could be done in the area of data mining and in identifying both the significance of- and gaps in- available data. It may not be so much a matter of releasing data as finding it in order to release it. The Arkansas Center of Excellence will establish a program seeking widely distributed data using advanced information management tools, particularly those associated with bioinformatics and modeling.
- Most importantly, the effort would engage the research community in an effort to establish a data repository. It would also require a validation and information arraying capability, another part of the Arkansas vision. This step would be followed by sharing and peer review, leading to the refinement of a nanotoxicology research plan.

(8) What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

- Providing much less expensive, more rapid tools to demonstrate safety early in the process of development will reduce the huge barriers of uncertainty, and thus encourage investors.
- Stronger grant programs for small businesses to either validate their technology or demonstrate safety should be considered.
- Incentives for entrepreneurial development at the universities might be considered. If, for instance, a new grant program were to be established for validation and safety testing of promising products, intellectual property may become more recognizably valuable more quickly. This may also be attractive to the venture capital community.

<u>WORKFORCE DEVELOPMENT</u>:

(9) What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

- Many entrepreneurs and scientists are unfamiliar with both the policy and the science required to obtain product approval. Therefore, the Arkansas Center of Excellence provides programs in Regulatory Science including a Certificate program, a Masters in Public Health focused on Regulatory Science and a Masters in Regulatory Science.

- If this Center of Excellence could receive federal funding, the educational component could be developed fully and also expanded to other campuses and sites with individual programs and/or feeder programs. The University of Arkansas at Pine Bluff, an HBCU in the Lower Mississippi Delta (and very close to NCTR) has offered a Bachelors degree in Regulatory Science for several years.
- This program is designed to be a part of a feedback loop in association with researchers, regulators and entrepreneurs to provide students with experience handling current issues. It incorporates this educational program into a policy review group that ties all of the programs together. Using that approach, as researchers and entrepreneurs work through the regulatory process, barriers found, approaches discussed and policy solutions may be matters for class discussion. Students may then have the opportunity to analyze identified problems and recommend policy and procedural changes that would be incorporated into reports and meetings with the federal agencies.

(10) What roles should community colleges play in training the bioeconomy workforce of the future?

- Community colleges could build construct small versions of facilities used in the bioeconomy for training purposes. This would allow them to instruct the traditional "trades" of pipefitters, electricians, mechanics and others to understand issues related to areas like biofuel production, bioconversion, reaction chambers, etc. The effort would focus on training current students, but also vigorously focused on re-training unemployed workers.
- Community colleges could work more vigorously with high schools to design programs that begin in the high schools and continue into the community colleges to train students for the type of work mentioned in the previous bullet. Such programs would also provide the opportunity to begin developing entrepreneurial interests in high school, and perhaps help students understand the need for STEM courses and develop interest in them.

(11) What role should the private sector play in training future bioeconomy scientists and engineers?

- More participation by the private sector is essential. In all of our training programs, particularly considering today's pace of technological development, the private sector must be available to give-real time examples of issues. It will also be important for the private sector to have a forum for evaluating various training programs with a feed-back loop to assure that graduates meet their needs.
- The private sector may be asked to allow access to facilities, equipment and expertise when efficiency indicates that such use would be in the best interest of the overall effort. By doing so, the private sector will enhance their voice in guiding the training programs.

(12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

- It is important to introduce the concept and the mindset for entrepreneurship early in the educational process and to continue it throughout. The county in which NCTR resides is developing a program in which high schools, a community college and a university (UAPB) combine resources to stimulate students, encourage entrepreneurialism, and engage faculty, postdocs and graduate students.
- NCTR participates vigorously with training, especially with its adjacent universities, primary among which is UAMS where many scientists serve as adjunct faculty, but also has very strong international participation. As this role increases, there will be more graduate students, post-docs, and faculty participating in NCTR research activities. The government might review incentives to determine if they are sufficient for assisting the process of commercialization.

REDUCING REGULATORY BARRIERS TO THE BIOECONOMY:

(13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are

a) slowing innovation, and

This effort is larger than one focused on a specific regulation. It encompasses an entire range of regulations enforced by FDA. Toxicology studies are often very time-consuming, especially if they require animal studies. Their results often require sophisticated statistical analysis, adding to the time required, but also adding significant uncertainty. Long time periods mixed with uncertainty become huge barriers to potential investors and certainly slow innovation.

b) could be reformed or streamlined while protecting public health, safety, and the environment.

- The entire NCTR mission is focused on public health. The re-direction of research is needed to assure protection of the public health. Part of that mission includes getting life-saving and life-improving therapeutics to the public as quickly as possible. Everything in this reply is directed to that end.

(14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system?

- Reducing the uncertainty in the approval of drugs, crop treatments, alternative fuels and chemicals as is the goal of the Arkansas Center of Excellence in Regulatory Science would be an enormously effective step.

(15) (a) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement?

In addition to funding of the science that provides the bases of regulatory review …and therefore product marketability… the Arkansas Center of Excellence in Regulatory Science is piloting a list of such improvements as previously listed.

(c) What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

In additions to re-thinking scientific funding priorities;

- Finding ways in which industry is not threatened by a process of sharing data and working to establish safety standards. Such a process would need to be carefully crafted to protect proprietary developments, and clearly not all data would be available for sharing, but making industry a partner in standard-setting would provide a base incentive.
- Looking for ways to apply resources being down-sized from other activities to help with this effort. For example, DoD may have enormous expertise in developing computer models of complex data. The Arkansas experiment is working to find ways to make this happen. Perhaps more capabilities could be matched to more needs.
- There are many known toxicity issues to be resolved in the realm of nano-medicine. However, the same or similar issues will likely arise when considering the future of nano-agriculture. Consider nano-fertilizer: This could revolutionize crop production to feed the world, but numerous agencies with numerous responsibilities would slow progress unless we are able to develop new models of cooperation—and new scientific and computer capabilities.

<u>PUBLIC-PRIVATE PARTNERSHIPS</u>:

(16) (a) What are the highest impact opportunities for public-private partnerships related to the bioeconomy?

To meet the "grand challenge" articulated in this response, public-private partnerships are essential and central to our Center of Excellence. It involves all of us working together, dedicated to finding new solutions and approaches...

(b) What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

- An over-arching goal is the safety of the public. The participants in this activity know up front, that there will be no short-cuts that risk harm to the public. The effort will be to find smarter ways to achieve the essential level of safety.
- The second goal is related to the first. The best interest of the public is not served if life-saving or otherwise helpful therapies or products are kept from them. Accordingly, a second goal is to facilitate the commercialization of such products.
- Diverse groups are engaged to support the entrepreneur.
    - As an example, Arkansas has funded a very successful program run by WinRock International called Innovate Arkansas. In this program, a group of professionals help guide the development of business plans and provide advice and assistance in obtaining capital and overcoming other barriers.
    - Innovate Arkansas is but one example of the impact of one volunteer organization of professionals from across the state who are very much involved in this Arkansas experiment. That group, Accelerate Arkansas has created not only Innovate Arkansas, but also the Arkansas Research Alliance, the Risk Capital Matching Fund, a STEM fund and numerous tax credits, teacher loan forgiveness programs and many others. This resource of over 70 volunteers is a major asset Arkansas offers to participate and lend experience to the Arkansas experiment. It is an indication of a spirit of cooperation and participation that can solve even the most difficult problems.

(17) (a) What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them?

- This reply has previously identified the opportunity for pre-competitive collaboration in safety standard-setting. It should support regulatory science and it should pull agencies together. Participating in the Arkansas Center of Excellence to pilot new ideas would be a helpful approach.

(b) What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector?

- We need only look to our global competitors to see that they are not following our model, and their success rates seem to be astounding compared to future projections for our own. We simply must do some things differently. If we want to stimulate entrepreneurship, we must think and act with an entrepreneurial spirit ourselves.
- Another example is the level of success attained by NIST, both in innovation and in transferring their technologies to the private sector. Re-evaluating the technology transfer capabilities of these national labs at NCTR might have a huge impact.

(d) What are the barriers to such collaborations and how might they be removed or overcome?

- Clearly, anything that sounds like increased funding will be a barrier. The need may be a matter of re-direction rather than new funding. We believe that there is sufficient recognition by the biomedical industry that this issue would be understood and supported. We would hope for a non-partisan, industry-supported effort that recognizes this approach is the most practical, efficient, least expensive (because it is non-duplicative) approach to removing huge barriers to successful product commercialization.
- Public fear could be another barrier. Proposing that industry and government cooperate could be a rallying cry for those who fear possible consequences. Bi-partisanship directed to the ability to develop new technology into an economic stimulus will be important.

APPENDIX--Footnotes

1. NCTR is called to participate and lead many important international scientific activities including:
   a. Joint FAO/WHO Expert Committee on Food Additives (JECFA)
   b. International Agency for Research on Cancer (IARC) of WHO
   c. National Institute of Food and Drug Safety, Republic of Korea
   d. Several universities in China
   e. The fact that there are over 50 postdocs and other PhD's from across the world at NCTR
   f. NCTR hosted a Global Summit on Regulatory Research in Little Rock, August, 2011 attended by over 40 scientists from 17 different countries representing Asia, Australia, Europe, Africa, South America and Canada
   g. Many, many university collaborations too numerous to list--all over the world
2. NCTR is described at http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/ucm2006206.htm
3. The Memorandum of Understanding is at http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm267896.htm
4. The Collaborative Supplemental Agreement can be emailed upon request from arnorris@swbell.net
5. The report may be found at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf The discussion relevant to this point begins on page 26. The subcommittee was chaired by **Gail H. Cassell, MS, PhD, DSc (Hon)**, Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company
6. Transcript of the May 30, 2008 Science Board meeting. http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4365t1-01.pdf beginning on p. 94 and continuing at http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4365t1-02.pdf/ on pages 21-24.

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December 8, 2011-by e-mail to bioeconomy@ostp.gov

RE: Comments to OSTP on National Bioeconomy Blueprint

TO: Office of Science and Technology Policy (OSTP)

In response to your Request for Information (RFI), the American Society of Agronomy (ASA), Crop Science Society of America (CSSA), and Soil Science Society of America (SSSA) recognize the importance of developing sustainable bioenergy and bioproducts sectors. Our more than 18,000 member scientists, graduate and undergraduate students from academia, federal government, industry and consulting sectors are involved in public and private partnerships, aimed at developing the next generation of cellulosic biomass, which span the continuum from basic (discovery) research through laboratory and field phases whereby our more than 14,000 crop consultants transfer the newly developed technologies, seeds, and vegetative materials to our nation's farmers. Combined, these efforts will aid America to reach the Renewable Fuel Standard challenge of increasing the volume of renewable fuel required to be blended into transportation fuel to 36 billion gallons by 2022.

With that goal in mind, Agronomists conduct research and develop technical approaches for increasing the efficiency of biofuel feedstock production systems. Crop Scientists contribute to advances in ethanol-based and cellulosic feedstocks and develop sustainable cropping systems. Soil Scientists perform research identifying methods to develop sustainable production systems that sequester greenhouse gases and identify soil-borne microorganisms optimal for use in conversion processes for biofuel production. Together, ASA, CSSA, and SSSA and its member scientists, educators, extension agents and consultants present a holistic perspective on best management approaches for biomass feedstock production and generate data and models needed for life-cycle analysis.

1) Identify one or more grand challenges for the bioeconomy in agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

Grand Challenge 1: Workforce and STEM Education Training
There are two main grand challenges to the success of the bioenergy sector. The first pressing challenge is the training and deployment of a qualified workforce for the bioenergy and bio-products industries. These industries require personnel with a diverse and transformative set of skills ranging from crop physiology and plant breeding to economics. Professionals and scientists are needed, who can offer consulting services, develop new feedstocks appropriate to conversion technologies, and continually refine the approaches for producing bioenergy crops and cropping systems.

Research, education, and extension programs within the United States Department of Agriculture Research Education and Economics Mission Area are currently in place that help to develop

educational and training materials appropriate to the needs of the bioenergy sector. ASA, CSSA, and SSSA urge the federal government to acknowledge and build upon the essential research conducted in such programs to build better Science, Technology, Engineering, and Mathematics education approaches that support the training of the next generation of experts who will be essential for developing and shaping the bioenergy sector.

We suggest that more university-industry partnerships at the bachelor, master, and Ph. D. levels occur via scholarships, fellowships, or internships. These could be federal or joint federal-privately funded programs. More emphasis on recruitment needs to occur by interacting with guidance counselors and high-school level educators so that students enter the pipeline early, at the high-school level. Community colleges will play a significant role in training students for the industry because not all jobs will require technical training at or above the bachelor level. Further development of the science-business interface is needed to educate faculty, students, and post-docs about commercialization strategies, including the marketing of innovative ideas for the purpose of acquiring capital, venture or otherwise. Federal support for better use of university-based, industry-supported innovation incubators would help to advance the development of the science-business interface.

Grand Challenge 2: Market Feasibility

The second challenging issue is the need to shape the development of the marketplace so that the consumers' demand is obvious to farmers. This means making the economic benefits of feedstock production clear and easy to understand. The cellulosic sector, for example, is significantly hampered by limited supplies of biofuel feedstock resulting from low product demand. Market barriers include: feedstock availability, competitive uses, and cost; large capital investment required for conversion facilities; and an inadequate supply-chain infrastructure. The ASA, CSSA, and SSSA recommend that private-public partnerships be identified and supported which take concrete steps to overcome these challenges.

Possible solutions to this challenge include the development of local supply-chain processing centers that increase the efficiency of local production, harvesting, preprocessing, and storage of uniform biomass commodity feedstocks. These centers would be modeled after the existing grain handling systems, which include local grain elevators, and would remove cellulosic biomass pretreatment from the bio refinery, keeping it at a local level in the biomass processing center. By fully integrating supply chain logistics on a local level, a series of several smaller, geographically dispersed local processing centers would preprocess, pretreat, and densify available biomass locally before transport to a central biorefinery.

This approach maximizes the biofuel value chain at the local level while improving rural development. It also offers substantial benefits to cellulosic biofuel production including:

- alignment of biomass production with the scale of cellulosic biorefineries;
- efficient use of existing locally owned conventional equipment to store and handle densified biomass;
- reduced transportation costs;
- reduced biorefinery conversion costs; and
- development of biorefinery cooperatives that contract with local processing centers instead of individual farmers.

Our members see numerous opportunities for collaboration between public and private sectors to accelerate the development of the bioeconomy without compromising the long-term sustainability of economic, environmental, or social factors of the sector. The challenges before us are surmountable at the local level, and the economic and environmental opportunities associated with bioenergy production, especially those in rural areas, appear to far outweigh the uncertainties. We urge the Administration to support programs that are currently underway in the research portfolio which support research in biofuels production and development.

Grand Challenge 3: Challenges for Research
ASA, CSSA, and SSSA each developed grand challenges for research related to bioenergy production. The challenges are as follows:

- ***American Society of Agronomy Grand Challenge:*** Double global food, feed, fiber, and fuel production on existing farmland within the 21st century with production systems that: enable food security; use resources more efficiently; enhance soil, water, and air quality, biodiversity, and ecosystem health; and are economically viable and socially responsible. For more information about ASA's Grand Challenge, please view: https://www.agronomy.org/files/science-policy/asa-grand-challenge-2010.pdf

- ***Crop Science Society of America Biofuel Grand Challenge:*** Develop sustainable biofuel feedstock cropping systems that require minimal land area, optimize production, and improve the environment. As a result, there is a need:
    - to modify crop compositions according to processing requirements;
    - to increase yield in low-input production systems;
    - to understand plant response to changes in the environment, in tandem with changes to composition for accurate modification;
    - to understand the ecosystem services (carbon sequestration, water quality, wildlife habitat, etc.) from perennial bioenergy crop production on arable and marginal lands; and
    - to develop new production systems that thrive in low-input situations.

  For more information on the CSSA Grand Challenge related to biofuel production, please view: https://www.crops.org/files/cssa-grand-challenge-layout-7-2011-updated.pdf

- ***Soil Science Society of America Grand Challenge:*** Optimizing soil ecosystem services for greater food and energy security, water quality, and adaptation to and mitigation of climate change. For more information, please view: https://www.soils.org/files/science-policy/sssa-grand-challenge-2011.pdf

We recommend that research and extension priorities be fashioned in line with these grand challenges for research. In closing, we are pleased that the Administration is taking on this important task and appreciate the opportunity to provide comment.

Sincerely,

Ellen Bergfeld
Chief Executive Officer
American Society of Agronomy
Crop Science Society of America
Soil Science Society of America
Alliance of Crop, Soil and Environmental Science Societies
5585 Guilford Road, Madison, WI 53711

[redacted]

*The **American Society of Agronomy** (ASA) is a scientific society helping its 8,000+ members advance the disciplines and practices of agronomy by supporting professional growth and science policy initiatives, and by providing quality, research-based publications and a variety of member services.*

*The **Crop Science Society of America** (CSSA), founded in 1955, is an international scientific society comprised of 6,000+ members with its headquarters in Madison, WI. Members advance the discipline of crop science by acquiring and disseminating information about crop breeding and genetics; crop physiology; crop ecology, management, and quality; seed physiology, production, and technology; turfgrass science; forage and grazinglands; genomics, molecular genetics, and biotechnology; and biomedical and enhanced plants.*

*The **Soil Science Society of America** (SSSA) is a progressive, international scientific society that fosters the transfer of knowledge and practices to sustain global soils. Based in Madison, WI, and founded in 1936, SSSA is the professional home for 6,000+ members dedicated to advancing the field of soil science. It provides information about soils in relation to crop production, environmental quality, ecosystem sustainability, bioremediation, waste management, recycling, and wise land use.*

American Veterinary Medical Association

Association of American Veterinary Medical Colleges

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December 8, 2011

Mr. Ted Wackler
Deputy Chief of Staff
Office of Science and Technology Policy
via E-mail only to: bioeconomy@ostp.gov

RE: REQUEST FOR INFORMATION: BUILDING A 21ST CENTURY BIOECONOMY

Dear Mr. Wackler:

As the national veterinary professional association representing more than 83% of US veterinarians, and the nation's sole representative for veterinary medical colleges, departments of comparative medicine, and departments of veterinary sciences, the American Veterinary Medical Association (AVMA) and Association of American Veterinary Medical Colleges (AAVMC), respectively, write this letter to provide the Office of Science and Technology Policy (OSTP) with our input regarding development of a National Bioeconomy Blueprint.

We, the AVMA, which represents all aspects of the veterinary medical profession, including biomedical and comparative medical research; private and corporate practice; and academic, industrial, governmental, military, and public health services; and the AAVMC member institutions, with specific expertise and engagement in comparative medicine, offer the following comments as responses to many of the questions posed in the Request for Information referenced above:

- Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.
  - Development and implementation of improved and rapid diagnostic, therapeutic, and prevention (e.g., vaccination) strategies for animal diseases, and in particular zoonotic diseases and diseases with the potential to negatively impact food security, that will limit their economic impact, prevent their spread from animals to animals and between animals and humans, and protect against their recurrence.

- Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?
  - Application of functional genomic, transcriptomics, and proteomics systems biology and analyses of infectious, parasitic, and metabolic diseases of livestock species to develop predictive biology approaches for discovery of the next generation of diagnostics, vaccines, and pharmaceuticals.
  - Technological and personnel approaches to improve food safety and science-based risk analysis.
  - Development of multipathogen and multimodality multiplex handheld diagnostics for use in major livestock species, including systems to detect emerging infectious and parasitic pathogens and developing antimicrobial resistance.
  - Increasing the understanding of potential impacts of climate change on animals and ecosystem health

  - Development of a scientific knowledge base regarding judicious therapeutic antimicrobial use, to include enhanced risk-analyses processes to determine actual risks of antimicrobial resistance resulting from use of antimicrobials in animal agriculture.
  - Development of a scientific knowledge base regarding judicious therapeutic antimicrobial use, to include enhanced risk-analyses processes to determine actual risks of antimicrobial resistance resulting from use of antimicrobials in animal agriculture.
  - Development of practical processes to safely filter, inactivate, or degrade pharmaceuticals and personal care products present in the nation's waters, as well as prevent entrance of such substances into the nation's waters.
  - Development of innovative and efficacious animal waste management systems and procedures to improve environmental quality.
  - Strong coordination and collaboration among all tiers of public health, agriculture, and animal management agencies to address climate change issues.
  - Development and validation of appropriate animal models to facilitate federal regulatory approval of medical devices, therapeutics, diagnostics and vaccines for animal and human diseases

- The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?
  - Increased utilization of spontaneous diseases in domestic animals (e.g., dogs, cats) as models of human diseases.

- What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.
  - Premature emphasis on the commercial potential of basic research activities places unnecessary costs on researchers and research institutes. It would be far more prudent to put effort into commercialization only after sufficient progress has been made on a research project to warrant potential commercialization.
  - Commercial markets are increasingly demanding that products be developed for zero risk. However, few—if any—products, processes, or activities carry zero risk. A better understanding and acceptance of development for minimal or acceptable risk would help to remove this barrier and, potentially, result in development of increased number of efficacious and safe (but not zero risk) products.

- What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?
  - Allow full-time academic employees to serve as principal investigators (or at least co-principal investigators) of SBIR and STTR projects.

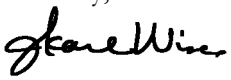
- The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?
  - The AVMA and AAVMC strongly support and affirm the recognition by the NIH of the role of veterinarians as scientists, educators, trainers, and collaborating partners in scientific research that takes a comparative, one-medicine approach to improvements in human and public health, as stated in the recent National Center for Research Resources (NCRR) 2009-2013 strategic plan (available at www.ncrr.nih.gov/strategic_plan/). Because contributions by veterinary basic scientists and clinical researchers will be critical for energizing the discipline of clinical and translational research across the country, the AVMA and AAVMC urge the continuation of

federal funding to support and expand opportunities for veterinary scientists and veterinary students to engage and participate in scientific education and training, research teams, and science policy and leadership roles, through the expansion of formalized training positions, broadening of debt-forgiveness clauses, and appointment on relevant federal agency committees and councils.

The AVMA and AAVMC also wish to use this opportunity to express our continued support for programs administered under the former National Center for Research Resources (NCRR) at the NIH, especially the Division of Comparative Medicine (DCM), which is now in the Office of the Director at the NIH. We define comparative medicine as a discipline in which the similarities and differences in biology among animals enhance the understanding of mechanisms of human and animal disease alike. In this way, biomedical research, clinical studies, and ultimately, therapy directed at experimentally induced and spontaneously occurring diseases in animals form the basis for animal models of human and animal disease. In other words, comparative medicine embodies translational medicine, and translational medicine— and, hence the DCM— will be a key component to implement and advance the National Bioeconomy Blueprint. Programs administered by the DCM provide research infrastructure and animal model support, as well as support for veterinarians in biomedical and public health research. The essential role of animal models and veterinary scientists should also not be underestimated in the formation and operation of the new NIH National Center for Advancing Translational Sciences, which will be essential to rapidly move basic research discoveries to benefit human and public health.

In closing, the AVMA and AAVMC believe the veterinary profession is uniquely positioned to be an active participant in both the process to develop a National Bioeconomy Blueprint and in its implementation. Veterinary medicine has the national responsibility to care for and protect animal health, and, in cooperation with other health and natural resources professions, to care for and protect public health, food systems, and environmental and ecosystem health. However, stewardship in these areas is challenged by new and re-emerging diseases that arise from characteristics particular to today's society, including globalization of commerce; commercialization and consolidation of food supplies; increasing transportation efficiencies; greater encroachments at animal-human-environmental interfaces; and the threat of bioterrorism. As such, traditional approaches will require innovative strategies and measures to successfully and effectively address these diverse risks into the future. The nation's veterinary profession, through the AVMA, and the nation's veterinary medical colleges, through the AAVMC, are eager to work with our colleagues in other disciplines and in both public and private sectors to meet these challenges head on through the development and implementation of a National Bioeconomy Blueprint. We thank the OSTP for this opportunity to provide comments. Should you have questions, please feel free to contact Dr. Elizabeth Sabin (esabin@avma.org; 800-248-2852, ext 6675) in the AVMA's Education and Research Division or Dr. Ted Mashima (tmashima@aavmc.org; 202-371-9195, ext 118) in the AAVMC's Academic and Research Affairs office.

Sincerely,



J. Karl Wise, PhD
AVMA Associate Executive Vice President
FOR: W. Ron DeHaven, DVM, MBA
AVMA Executive Vice President, CEO

Bennie Osburn, DVM, PhD, DACVP
AAVMC Interim Executive Director

Association of University Technology Managers®
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December 9, 2011

To Whom It May Concern:

On behalf of the Association of University Technology Managers (AUTM), I am pleased to submit second response to the Office of Science and Technology Policy Request for Information: Building a 21st Century Bioeconomy. This is in addition to the response we sent on December 6, 2011.

AUTM is a nonprofit organization with an international membership of more than 3,000 technology managers and business executives. These members come from more than 300 universities, research institutions, teaching hospitals, government organizations and businesses.

We believe that academic technology transfer can help harness biological research innovations to meet national challenges in health, food, energy, and the environment while creating high-wage, high-skill jobs. To do so, we must ensure technologies are afforded the smartest, most efficient path to development, allow for easier access of technology commercialization resources by federal employees and free up capital for development of technologies. Therefore, we are pleased to offer the following policy suggestions

Just Say 'No' to Free Agency

We are concerned about a recommendation in the recent report from President Obama's Council on Jobs and Competitiveness. The suggestion to allow research that is funded with federal dollars to be presented to any university technology transfer office, not just the one where the research has taken place (sometimes referred to as Free Agency) would actually slow the process of commercialization. The Free Agency concept would add a new layer of bureaucracy to the technology transfer process, including the need for agreements between the inventor's institution and the licensing agent which would add considerable time to the technology transfer process BEFORE marketing and licensing could even be started, as well as potentially reducing the inventor's share of royalties through management fees assessed by the licensing agent. The concept also assumes technology transfer offices would want to commercialize another institution's technologies, when in fact MIT, Stanford University and WARF (three of the largest and oldest technology transfer offices) have all publicly stated, "It would be inappropriate for us to handle inventions from inventors outside our own institutions, and we have no interest in doing so." The administration is right to recognize in the RFI that "It is a challenge to commercialize advances in the life sciences because of the risk…" The Free Agency approach to commercialization will create more risk in the eyes of companies which would normally invest in the technologies because untangling title and ownership would be more complicated and fraught with potential legal burdens

The National Research Council of the National Academies has looked this issue, and their finding is: "A persuasive case has not been made for converting to an inventor ownership

or “free agency” system in which inventors are able to dispose their inventions without university administration approval. If evidence is developed suggesting that either would be more effective than the current system, other significant practical consequences and policy considerations would have to be considered, such as the potential for conflicts of interest and adverse effects on public accountability.” [1]

It is imperative the Administration opposes any proposed policy or legislation that would enact a Free Agency model.

Easy Access to Technology Commercialization Resources
AUTM already has a networking and education infrastructure in place to help government agencies that generate intellectual property, such as the NIH, NSF, Department of Defense, Department of Energy, NASA and the federal labs; however, regulations make it difficult for those working in these agencies and labs to join AUTM and other professional societies. This forces those who are employed by the federal government to make the tough decision to pay for memberships out of their own pocket. Preventing these agency employees from joining AUTM, or any professional society, blocks their ability to participate in online and in-person education events at the more affordable member rates. While employees of government agencies can certainly attend conferences, they can only do so by paying the higher nonmember rate, which means they must stretch already limited travel and education budgets. They also miss the opportunity to take advantage of free member benefits such as immediate online networking and sample policies and procedures in our *Technology Transfer Practice Manual*. In addition, AUTM is launching its Global Technology Portal (GTP) at the end of 2011, and this portal allows AUTM members to list technologies available for licensing for free. Because government agencies are not allowed to join professional organizations such as AUTM, government agencies can't maximize their ability to promote technologies they have available for licensing via the GTP, which means fewer technologies will be commercialized and fewer companies and jobs will be created. AUTM already has the programs, infrastructure and community in place. Now the Administration needs to reverse the rule that does not allow for it to pay employees' membership dues to professional societies.

In addition, the Office of Government Ethics (OGE) has recently proposed a rule change that would impact government employees’ attendance at trade associations meetings. In short, the proposed rule would prohibit executive branch employees (including those working for agencies) from accepting *complimentary* registrations to meetings held by 501(c)6 associations. AUTM opposes this rule change, as we feel prohibiting free attendance at trade association meetings is counterproductive to providing the education and networking opportunities vital to commercialization.

Free up Capital Through Targeted Tax Credits
The success of a startup company or small business often hinges on access to small amounts of capital. Making the Research and Experimentation Tax Credit permanent for these businesses will be a welcome relief as will the increased financial support in the Small Business Jobs Act, which the President signed into law last year.

Federal tax credits should be provided to industry to encourage businesses and venture partners to leverage university technologies and startup venture opportunities.

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[1] Managing University Intellectual Property in the Public Interest, Committee on Science, Technology, and Law Policy and Global Affairs, National Research Council of the National Academies, p. 73

Clearly, the members of AUTM share the administration's interest in innovation. We share the priority of accelerating commercialization of university technologies, creating a stronger bioeconomy and are willing partners in seeking out new methods and improving upon standard practices. Thank you for the opportunity to respond to this Request for Information.

Sincerely,

Robin Rasor, CLP, RTTP
President

Four Proposed Grand Challenges, and Related Initiatives to Improve Healthcare Delivery in the 21st Century BioEconomy

Draft Document for Discussion

December 6, 2011

James R. Gorman, M.D., Ph.D.
Healthcare Innovation Laboratory
Natick, MA
[redacted]

Note: This draft document was developed on December 6, 2011, shortly before the submission deadline. As a result of the limited time available for preparation, only one literature reference has been included. Additional literature references may be made available upon request.

Proposal I: Pediatric Drug Development Fund (PDDF): An Expanded Pre-Competitive Public-Private Partnership to Discover, Develop and Commercialize Pediatric Drugs

I. Outline of Proposal
   a. Background and Overview: Pediatric Drug Development Fund (PDDF) would oversee prioritization of diseases, targets, and the most important drugs for development and commercialization for pediatric populations.
   b. Regulation: Change FDA regulations to allow companies to obtain exclusivity by contributing appropriate fees to Pediatric Drug Development Fund, without conducting pediatric trials. Allow pharmaceutical sponsors of high priority drugs to obtain exclusivity by developing drugs, in some instances with support from PDDF.
   c. Mission of PDDF: Fund and authorize PDDF to prioritize, develop, manufacture and distribute highest priority pediatric drugs.

II. Background and Overview

a. Pediatric populations continue to be underserved. Too few pharmaceutical formulations are tested in and optimized for use in infants and children. This creates a substantial burden on pharmacists, health professionals, payers, parents and children.

i. Commercial investment is hindered by:

1. small patient populations, highly fragmented due to different needs in different age groups;
2. different pharmacology and formulation and delivery needs in neonatal, infant/toddler, children, and adolescent populations;
3. ethical and operational issues in conducting trials, resulting expenses and other related barriers.

ii. Many legacy approved products lack the pre-clinical, pharmacologic, pharmacokinetic, safety, and efficacy data required to guide safe appropriate use in children.

iii. Some commercialized products are not available in the appropriate formulations to support use in one or more pediatric sub-populations.

b. Issues with Incentives Under the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

i. Background: In order to obtain 6-month market exclusivity extension for adult markets, sponsors agree to conduct studies in children.

ii. Issues with trial requirement in exchange for exclusivity extension:

1. Critics and observers report that sponsors may not be motivated to seek commercialization of pediatric products.
    a. May result in investment of minimum resources necessary to meet the commitment in order to gain exclusivity;
    b. Studies may be conducted that are inadequately designed to produce interpretable efficacy and safety data. Such studies may simultaneously meet requirements for exclusivity, while failing to result in development and commercialization for pediatric populations, with robust safety and efficacy data from well-designed trials, and formulations optimized for infants and children.
    c. Critics allege that children are sometimes subjected to trials participation with its inherent risks, without the generation of interpretable data appropriate to guide drug development.

2. The incentive process is not designed to identify and support development of the most urgently needed drugs.
    a. The process only stimulates development of pediatric versions of new, branded drugs.
    b. Many needed drugs are generic, or low margin; their development and reformulation for children will not be stimulated by current exclusivity incentives.
    c. Some new drugs are simply not developed due to variables including market size and pricing, potential liability, time to market, and so forth.
3. Summary: The current system does not adequately prioritize and facilitate development of the most needed drugs for pediatric populations. It subjects sponsors to a requirement to conduct clinical trials in order to achieve an unrelated commercial objective of a 6-month extension of market exclusivity. While this incentive has resulted in increased commercial availability of some drugs for children, the process is alleged to result in substandard trial conduct, and is not designed to optimize identification and development of the most urgently-needed drugs and formulations for infants and children.

III. Recommended change in regulations:
- a. Offer sponsors the option to pay an appropriate multi-million-dollar fee in order to obtain 6-month additional market exclusivity.
- b. Fee designed to be substantial, but low enough to provide incentive for companies to pay fee.
- c. By paying this fee, they would obtain 6-month exclusivity extension, without incurring an obligation to conduct pediatric trials.
- d. Fees would be used by Pediatric Drug Development Fund (PDDF) to fund prioritization and development of the must urgently needed pediatric drugs.
- e. Sponsors wishing to obtain the exclusivity extension by developing and commercializing their <u>own</u> drug for pediatric populations, rather than by paying the PDDF fee, would be required to submit a proposal to the FDA outlining the need for the drug in children, and a plan for robust development, formulation, and commercialization. If the plan is approved, then the exclusivity extension would be allowed, contingent upon the sponsor actually obtaining pediatric labeling and making an appropriate formulation commercially available for pediatric use.
- f. Fees and exclusivity period could be increased or reduced depending upon the number of needed pediatric formulations commercialized (e.g. NICU, oral liquid formulation, and so forth).

IV. Role and Activities of Pediatric Drug Development Funds

a. Prioritization Process: Prioritize standard of care and unmet need, defining the most urgently needed pediatric medicines and formulations; draw from and collaborate with existing efforts (NIH, WHO and other organizations' lists of drugs needed for pediatric development).
b. Formulation Technology Platform Development
    i. Laboratory effort to develop improved formulation technology
    ii. Focus areas to include catalog of approaches for structural classes and delivery routes.
    iii. Specific Technologies: open source database and technology pool including solvents and excipients, algorithms, modeling software, and testing platforms.
c. Conduct pre-clinical and proof-of-concept studies in the highest priority areas:
    i. Outsourced through NIH, FNIH or other agencies, or funded via a direct grant-awarding function of the PDDF.
    ii. Clinical Development
        1. Develop improved clinical trial designs, instruments, and measurement tools for pediatric clinical studies
        2. Work with NIH and academics to organize an improved pediatric clinical trials consortium with patient registries
        3. Provide a state-of-the-art clinical trial management group
        4. Objectives:
            a. Prioritization process drawing upon published and primary comparative effectiveness research.
            b. Only medicines that are standard of care or will improve the standard of care would be developed.
            c. Medicines and classes shown to be ineffective or that do not have significant potential to provide substantial clinical or cost benefit over existing therapies will not be further tested in children.
            d. Study designs must be state-of-the-art, and designed to provide data needed to guide pediatric therapy.
d. Distribution: Organize a wholly owned Low-Profit LLC (L3C) or other subsidiary entity that will organize the manufacture and distribution of drugs developed by PDDF.
    i. produce low profits that can attract investment by foundations and other investors, while promoting the educational mission of the institute.
    ii. provide evidence-based information to pediatricians, patients and families;
    iii. direct profits back into PDDF to support its mission to develop, manufacture and distribute evidence-based pediatric drugs.

V. PDDF: Stakeholders likely to support initiative

a. Pharmaceutical sponsors: obtain exclusivity extension through a fee mechanism, avoiding the need to conduct costly and risk pediatric studies for drugs they do not wish to commercialize in children.
b. Payers, providers, hospitals:
    i. Benefit by having available the most urgently-needed pediatric drugs, with robust data packages;
    ii. Decrease the commercial influence on prescribing habits in pediatric populations:
        1. distribution would be performed by L3C responsible for carrying out the educational mission of the organization;
        2. profits resulting from carrying out the low profit manufacture, education and distribution function would flow into PDDF to further the mission.
c. Patients and families:
    i. Benefit by having drugs tested, formulated, reasonably priced.
    ii. Benefit by reducing unnecessary and poorly designed trials.
    iii. Benefit by gaining access to the most urgently-needed medicines, supported by robust evidence.
d. Government agencies:
    i. Food and Drug Administration (FDA), CMS/HHS, NIH, and related entities such as Reagan-Udall Foundation, Foundation for the NIH, and others benefit through making available to the public the most effective, safe, cost-effective drugs.
e. Philanthropic organizations and foundations benefit by meeting the healthcare needs of children.

Proposal 2: Put Pharmaceutical Marketing Reps and Allied Health Professionals to Work Promoting Evidence-Based Standards of Care, Including Use of Generic Drugs.

A. Develop marketing organization to detail standard of care and evidence-based medicine to physicians.
    a. Thousands of pharmaceutical marketing professionals have been laid off as industry has reduced costs.
    b. New sales force would promote best practices, including generics.
    c. Organization would analyze the cost versus efficacy and safety of new branded medications versus older generic medicines, educate physicians on the comparative data.
B. Infrastructure:
    a. Analysis center (immediately analyze new medications in terms of cost and benefit).
    b. Marketing center (create high quality materials and training)
    c. Sales Force
        i. Outreach to physicians and health professionals
        ii. Outreach to patients with balanced information
    d. CME Organization (conduce CME online, in office calls, and at professional meetings)

Proposal 3: Require Balanced, Standardized Presentation of Risks and Benefits for High Cost and/or Low Evidence Interventions funded by CMS.

1) Categorize CMS-funded procedures on the basis of cost versus evidence of efficacy. For procedures that are medium to low evidence, require that each patient to whom a CMS reimbursed procedure is recommended, undergo a standardized balanced presentation of risks and benefits prior to electing to undergo the procedure.
2) In one recent example, designed as one component of the Spine Patients Outcomes Research Trial (SPORT), patients to whom disk removal surgery was recommended, were required to view a video presenting a balanced discussion of the risks and benefits of the surgery. More than 50% of these subjects declined to undergo surgery, electing instead to undergo "watchful waiting" (Weinstein JN, Tosteson TD, Lurie JD, et al. *Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial*. JAMA 2006;296:2441–2450).
3) Develop a series of standardized risk-benefit videos, and train/retrain appropriate health and allied professionals to present the videos.
4) Stakeholders: Those whose care would improve and/or costs would go down
    a. Academic Medical Centers and Hospitals/Delivery Systems
    b. Corporations: Large consumers of healthcare.
    c. Government Organizations funding healthcare.
    d. Patient groups consuming healthcare.
    e. NGOs

Proposal 4: Develop Central 2nd Source of Manufacturing for Critical Chemotherapy Drugs at Risk for Shortages; Create Shared Stockpile to Address Shortages

Request for Information: Building a 21st Century Bioeconomy

QIAGEN Response

Response submitted by:

Dietrich Hauffe, Vice President - Head of Life Science and Applied Testing Business, [redacted]

With contributions from:

Willem Folkerts, Director, Head of Europe and North America Life Science Regional Marketing, member of Americas Management Council, QIAGEN Inc., [redacted]

Matthew Sammons, Specialist, Recruiting & Employer Branding, QIAGEN Inc., Human Resources, [redacted]

Maja Owens, Manager, Head of Competence Center, Professional Training and Organizational Development, Human Resources Americas, QIAGEN, [redacted]

Lindsey Howard, VP, Quality Assurance North America, QIAGEN Sciences LLC, [redacted]

Dirk Loeffert, Ph.D., Vice President Head of Sample & Assay, R & D, QIAGEN, Hilden, Germany, [redacted]

Introduction:

QIAGEN respectfully submits this document in response to the Notice of Request for Information (RFI) by the Science and Technology Policy Office on October 11, 2011 as a means of providing input into the development of the National Bioeconomy Blueprint.

Note: The responses to the individual questions in the RFI are intentionally brief to ensure the most important points are captured. In addition, the responses are brief to maximize OSTP's ability to capture and synthesize the volume of input that is expected to be received in response to this RFI.

Corporate Information:

QIAGEN (www.qiagen.com) is the leading provider of sample and assay technologies. Sample technologies are used to isolate DNA, RNA, and proteins from any biological sample. Assay technologies are then used to make specific target biomolecules, such as the DNA of a specific virus, visible for subsequent analysis.

We have developed and market more than 500 consumable products and automated solutions. The company provides these products to molecular diagnostics laboratories, academic researchers, pharmaceutical and biotechnology companies, and applied testing customers for purposes such as forensics, animal or food testing and pharmaceutical process control. QIAGEN's assay technologies include one of the broadest panels of molecular diagnostic tests available worldwide. This panel includes the Digene HPV Test, which is regarded as a "gold standard" in testing for high-risk types of human papillomavirus (HPV), the primary cause of cervical cancer, as well as a broad suite of solutions for infectious disease testing and companion diagnostics.

QIAGEN employs more than 3,000 people in over 35 locations worldwide, with over 1000 employees in four sites and remote locations throughout the United States. Our sales exceed $1.0 billion globally.

Grand challenges:

OSTP question:

(1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

QIAGEN response –

Grand challenges for the bioeconomy include the development and expanded use of cost effective molecular based clinical diagnostics for:

- Disease Prevention - screening of non-symptomatic patients to detect risks for specific diseases such as cancer.
- Disease Profiling - testing of symptomatic patients to determine the type and severity of an infection.
- Personalized Healthcare – testing of pre-diagnosed patients to guide treatment decisions and use of medicines.
- Point of Need testing – testing in non-laboratory settings such as doctors' offices or field based sites.

Through early detection, appropriate profiling, personalized healthcare, and point of need testing, hundreds of thousands of lives can be saved and health care costs can be reduced significantly.

Concrete steps that can be taken to achieve these goals include:

- Effective and efficient federal regulatory processes that work in cooperation with academia and industry to appropriately balance the risk/benefit of a test or treatment.
- Enhanced and optimized funding programs spanning from basic research through discovery and translation to a commercially viable product with a focus on those disease states of greatest impact to the population. These funding programs should incentivize the research and industry community based on speed of development, utility, and impact of a given diagnostic or treatment.
- Enhanced public/private partnerships that foster innovation while appropriately protecting the Intellectual Property created as a result of these partnerships.
- Improved public and private cooperation in creating awareness of new molecular based diagnostics through the communication of best practices and clinical outcomes.

In addition to the expanded use of cost effective molecular based clinical diagnostics, grand challenges for the bioeconomy exist in the development and expanded use of cost effective molecular based tests in applied applications including:

- Forensics – increased use of genetic "fingerprinting" to help solve criminal investigations and better ensure the safety of the population.
- Food safety – quickly and accurately identifying food contamination from pathogens in all stages of the food cycle – from "farm to fork".
- Veterinary diagnostics - quickly and accurately preventing, profiling, and treating diseases within our nation's livestock.

Concrete steps that can be taken to achieve these goals include:

- Expanding upon the existing National Institute of Justice funding programs for state and federal crime laboratories to facilitate the acquisition of state of the art molecular based methods including automation; as well as persuade CODIS SSO to adopt a requirement that all patent covering STR Loci must be disclosed and/or made available for licensing.
- Streamlined and more efficient federal regulatory processes from FDA and USDA to quickly approve and create awareness about new technologies that provide greater sensitivity and specificity for detecting pathogens and disease while decreasing the overall cost of testing food or livestock.

Research and development:

OSTP question:

(2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

QIAGEN response:

From our routine analysis and according to publically available Health and Human Resources information (http://report.nih.gov/rcdc/categories/), there are 229 research/disease areas that receive funding. The top ten funding priorities are:

- Clinical Research
- Genetics
- Prevention
- Cancer
- Biotechnology
- Neurosciences
- Infectious Diseases
- Brain Disorders
- Women's Health
- Behavioral and Social Science

These ten areas receive approximately 43% of current funding. QIAGEN generally supports the current prioritization of funding given that these areas are pragmatic in nature and provide for clear utilization of emerging genetic based analysis leading to appropriate treatment of disease. As mentioned earlier in the corporate information, QIAGEN has been focused on providing state of the art clinical diagnostics, including the digene HPV Test, which is regarded as a "gold standard" in testing for high-risk types of human papillomavirus (HPV), the primary cause of cervical cancer, as well as a broad suite of solutions for infectious disease testing and companion diagnostics. In addition, QIAGEN plays a key role in providing the tools (instruments and reagents) for collection and analysis of nucleic acids from all sample types that are required in all areas of research currently prioritized by HHS.

QIAGEN would suggest a continuing shift in research funding to the area of companion diagnostics or personalized health care. FDA has already identified more than 30 different diagnostic target markers in the context of approved drug labels. As this number increases new molecular technologies will and must be developed to more accurately gauge the efficacy and safety of drugs in individual patients.

OSTP question:

(3) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

QIAGEN Response:

There are many challenges to high throughput research both technically and pragmatically. The researcher must balance high throughput with flexibility. Flexibility is needed based on sample type and source. Researchers must be provided access to next generation platforms that must take many types of biological samples (such as blood, tissue, or saliva) isolate and purify target molecules in a specific sequence and analyze these materials reliably and efficiently to provide useful results. It's clear that a balanced approach towards funding both high throughput and low/medium throughput platforms with flexibility areas is needed. QIAGEN has clearly recognized and validated this need for flexibility within the research community and as a result has developed and launched the fully automated QIAsymphony RGQ, which allows customers to use their own tests, as well as QIAGEN developed tests, to conduct basic or applied research as well as clinical diagnostics.

To specify a particular rallying point within the research community and industry is quite difficult and potentially limiting to the necessary creativity and innovativeness that is a hallmark of the existing US Bioeconomy. As mentioned previously within this document, personalized medicine has clear long term implications to healthcare outcomes and overall costs.

OSTP question:

(4) The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

QIAGEN response:

Recent developments in high throughput sequencing techniques has generated a wealth of new information on gene sequences whose functions are yet to be determined. Further analysis of those DNA sequences will likely be based on two major efforts: One route will consist of the comparative study of genomes and

structural genome information of other organisms mainly based on the same discovery technologies such as high throughput sequencing. A second approach will address the functional analysis of those gene sequences by means of investigating the regulatory network in which those genes may be involved as well as protein expression of gene sequences from cDNA libraries and using a variety of tools for protein analysis. This second approach will rely on the development of robust yet cost-effective tools that allow higher throughput analysis of expression levels of RNAs and proteins as well as their cellular localization and interaction with other regulatory proteins or nucleic acids in the context of the genome organization. Different technological approaches require highly standardized sample preparation techniques to reliably isolate and analyze RNAs and proteins or e.g. regulatory proteins bound to genomic sequences for which QIAGEN has developed a variety of highly standardized robust sample preparation technologies that can be also automated for higher throughput. Another core activity at QIAGEN focuses on validation of such regulatory gene networks with real-time PCR based array products for sensitive, reproducible and robust detection of gene expression levels or gene mutations within its biological context. QIAGEN believes that multidisciplinary projects and technology developments should be funded that focus on the elucidation of genome structure and its regulation as well as effects attributed to mutations or regulatory molecules such as miRNA or proteins bound to DNA regulatory regions and their modifications along with the development of software tools that can be employed to statistically evaluate the significance of gene functions and -interactions.

Moving life sciences breakthroughs from lab to market:

OSTP question:

(5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

QIAGEN response:

Barriers preventing the commercialization of biological discoveries include:

- Total available market – uncertainty in the final free market revenue contribution of a given discovery.
- Market accessibility – uncertainty in the inherent "pull" from the market versus the "push" required to generate revenue from a given technology.
- "Valley of death" - uncertainty in the ability of a technology to navigate over the period where academic funding stops and commercial funding starts
- Development costs – inherently expensive clinical trial costs required to validate sensitivity, specificity, efficacy, and utility.

- Regulatory complexity – navigating the complicated and at times unclear regulatory pathway
- Commercialization costs – extensive sales and marketing resources necessary to create awareness and uptake of a new technology.
- Intellectual property – inherent risks in rights of ownership of a given discovery

Specific steps that can be taken to address these barriers include:

- Stronger public/private partnerships with shared risk to market for a given discovery.
- Additional funding for translational research that bridges the current "valley of death".
- Federally guaranteed markets such as that created for biodefense vaccines.
- Streamlined regulatory processes.

OSTP question:

(6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?

QIAGEN response:

QIAGEN does not participate in SBIR or STTR programs. Enhancement of these programs to facilitate small business to larger business programs would be helpful. These programs may include risk mitigation approaches to better entice the larger entities to engage with small business.

OSTP question:

(7) What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

No QIAGEN response:

OSTP question:

(8) What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

QIAGEN response:

Challenges and responses are the same as those identified in OSTP Question (5).

OSTP Question:

Workforce development:

QIAGEN Summary Statement:

In order to create a technically-skilled workforce, education about bioeconomy (still quite a new topic/term) should start early and a foundation should be laid in High School. Potential employees need to learn very early on about career opportunities in bioeconomy. Additionally, education needs to be affordable for everyone who wants to pursue a college degree/academia education to ensure a high number of potential candidates for the bioeconomy workforce.

OSTP question:

(9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

QIAGEN response:

- Redesign programs to better meet current and future science and technologies needs in close cooperation with the private sector
- Universities might need to adapt their approach by including current business trends, development/technologies and more real life examples into their programs

OSTP question:

(10) What roles should community colleges play in training the bioeconomy workforce of the future?

QIAGEN response:

Community colleges are vital resources for manufacturing and technical associate positions within the biotechnology industry. By utilizing a model similar to the auto and aviation industry we can ensure the community colleges are producing students that have the right set of skills and training.

- Auto & aviation industries have provided engine schematics and blueprints to community colleges and trade schools for years so that students are learning how to build and repair actual engines. We can mimic this by providing our manufacturing and production procedures to professors so that

they can create curriculum that trains students in relevant procedures and methods

- Create a relationship with local community college professors and industry managers that ensure the curriculum develops broad skills necessary for entry-level work.
- By working with QIAGEN, BioReliance, and Human Genome Sciences, Montgomery County Community College in Maryland has developed curriculum that trains students using actual FDA regulated documentation and manufacturing procedures. The Biotechnology coursework includes learning procedures that are certified cGMP and cGDP by the FDA and is being reviewed every year to ensure the curriculum adapts to the needs of the industry.

OSTP question:

(11) What role should the private sector play in training future bioeconomy scientists and engineers?

QIAGEN response:

- Learn from educational standards/programs in other countries and how the private sector cooperates with academia, i.e. on the job training which is support by educational programs at college
- The private sector should influence and guide what their (potential) employees should learn by working closing with academia, influence their programs and sponsor education to develop a workforce according to their business needs

OSTP question:

(12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

QIAGEN response:

Several types of programs can be expanded or created to ensure this relationship.

- Capstone Programs – Industry problems or projects are given to a group of students (bachelors or graduate level) and are tasked with creating a solution to the problem. Monthly collaborative meetings are scheduled between the students and an industry Capstone Program Leader to ensure the team is working in the right direction for a solution. Final presentation is made at the end of a semester to the company and awards or scholarships can be awarded to students for their work.

- Beyond the Bench – Business skills are not generally included in Biological Sciences curriculum. Industry hosted online seminars or on-site presentations at places like the NIH or colleges and universities should be more prevalent to ensure students are knowledgeable about what is needed to start their own company, patent an idea or product, or pursue innovative new business concepts within biotechnology.
- Internships/Co-op Programs – Industry must provide more opportunities for students to work at companies while still in school. Internship programs can help reduce cost-per-hire, reduce required training time for entry-level employees, and provide the industry with a pipeline of young talent that is eager to learn. QIAGEN has successfully hosted 70+ students in the past 2 years and has been able to fill 8 full-time openings with "graduates" of our Internship Program. Of those students, 100% responded in surveys that they were better trained and more knowledgeable about careers within the industry, and 98% were better equipped with the tools and training it would take to land a position within the industry.

Reducing regulatory barriers to the bioeconomy:

OSTP question:

(13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

QIAGEN Response:

In vitro Diagnostic (IVD) Tests are currently treated by the FDA in the same way as other more invasive devices. Many diagnostics are even classified as Class III and require premarket approval, due to the lack of predicate devices. This in turn puts them under the same level of criticality and scrutiny as invasive devices like catheters, many of which are Class II devices. This is a direct impediment to innovation especially when compared to Europe.

The EU, under the IVDD directives, allows most diagnostic tests to be "self-declared". While it would be legislatively difficult for FDA to move to self-declaration, they could re-classify IVD assays to Class I and if need be issue special controls to insure the assays are developed under design controls as well as specific assay requirements. In this way the approval process would be closer to par with the EU but still maintain FDA oversight and audit authority.

OSTP question:

(14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

QIAGEN Response:

See (13)

OSTP Question:

(15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

As stated in (13) many new In vitro Diagnostics are slow to be implemented or adopted due to the hurdle created by the FDA Pre-Market Approval process. On the other hand independent testing labs are able to develop these same tests under CLIA without this regulatory burden but also without the same scientific rigor required for manufacturers. A potential solution would be to allow manufacturers to partner and supply these labs with well characterized component "sets" that are not characterized sufficiently to meet the hurdle for PMA "kit" approval but could be manufactured under full FDA cGMP controls. This could provide the laboratory with a much more rigorous and reliable product while accelerating a new assay technology to the market.

Public-private partnerships:

OSTP question:

(16) What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

QIAGEN response:

Public-private partnerships are essential to the efficient and effective commercialization of biological discoveries. As stated earlier in this document, a stronger and more defined sharing of risk/reward is needed to span the gap from the end of academic funding to the start of private funding. This could take the form of clear responsibilities and deliverables on each side of this translational research cooperation. Greater public contribution to offset risk could be rewarded by defined funding payments to the public institution should the commercialization of the biological discovery reach certain points. Clarity of intellectual property ownership

has also been a downfall of many public-private partnerships. Again, a more balanced approach towards risk/reward may be beneficial here as well.

OSTP question:

(17) What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

QIAGEN response:

The following barriers make pre-competitive collaboration difficult:

- Intellectual property ownership issues
- Lack of control
- Uncertain return and risk
- Commercialization uncertainty – sales and marketing channel management

The overriding issue is related to the risk/reward balance. Typically companies prefer to work within their own sphere of control. Having said this though, the companion diagnostic space may be an area where clear pre-competitive collaboration has been successful. There are numerous examples, including many within QIAGEN, where strong partnerships have developed across the pharma/diagnostic spectrum. These relationships are based on mutual need and benefit with enough clarity of intellectual property and commercialization approaches to make the relationship successful. Government has the opportunity to foster these kinds of relationships early since many of these markers are identified in academia and HHS could consider a provision for clear pre-competitive collaboration and appropriate milestones as a requirement in awarded grants.

In addition, meetings similar to the Annual PHEMCE Stakeholders Workshop and BARDA Industry Day (http://www.federalregister.gov/articles/2010/10/15/2010-26047/5th-annual-phemce-stakeholders-workshop-and-barda-industry-day) held in early 2011 are also a very positive in helping to build pre-competitive knowledge and linkages between the public and private sectors.

Initial Inputs from colleagues at
The Joint School of Nanoscience and Nanoengineering
for OSTP's RFI on the Bioeconomy

OSTP seeks comment on the questions listed below to inform the development of the National Bioeconomy Blueprint:

Grand challenges: President Obama has identified ``grand challenges'' as an important element of his innovation strategy, such as ``smart anti-cancer therapeutics that kill cancer cells and leave their normal neighbors untouched; early detection of dozens of diseases from a saliva sample; personalized medicine that enables the prescription of the right dose of the right drug for the right person; a universal vaccine for influenza that will protect against all future strains; and regenerative medicine that can end the agonizing wait for an organ transplant.''

(1) Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal.

12/09/11: Daniel J.C. Herr, [redacted], Chair - Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #1: On what a bioeconomy can learn and leverage from Nature

What clues and guiding principles can Nature and living biosystems reveal to us about the requirements and architecture of a thriving and sustainable bioeconomy? In the **Fabric of Life**, Fritjof Capra describes a robust living system, not as a collection of discrete and isolated components, but as an integrated network of interdependent systems, with dynamic and adaptive feedback processes. More than fifty years ago, Richard Feynman shared a vision for the hierarchical dimensional convergence between top down and bottom up science and technology. The next frontier is the horizontal reconvergence of complex, information rich systems across disciplines. Nature cares little about how or where we artificially draw disciplinary boundaries. In fact, one could argue that traditional siloed approaches to education, research, development, commercialization, nanomanufacturing, economics, environmental impact, history, communication, and art are rather unnatural. Siloed disciplines assume varying degrees of independence, which creates blinders to the reality of their intricate interdependencies and their dynamic and adaptive feedback processes.

Recommended Action #1: Support new research frontiers in convergent technologies, especially between disciplines that may seem to be unrelated, such as metabolic pathways and processes and sustainable economic networks. In another embodiment, consider research that explores linkages between the impact of environmental dynamics

on an ecosystem's evolution with adaptive models for local, regional, and global economic development, in a world of ever changing resource, environmental, workforce, technology, and political requirements and constraints. This vision calls for innovative and hands-on seed corn programs that leverage the interdependence of education, research, development, commercialization, nanomanufacturing, economics, environmental impact, history, communication, and art.

Research and development: R&D investments, particularly in platform technologies, can support advances in health, energy, the environment, and agriculture, and accelerate the pace of discovery in fundamental life sciences research.

(2) Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

12/09/11: Shyam Aravamudhan, [redacted] Assistant Professor, Department of Nanoengineering, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina
Daniel J.C. Herr, [redacted] Chair - Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #2a: On the bioeconomy in health applications
Health biotechnology, which is the use of knowledge of cell functions and genetics at the molecular level, including the understanding of DNA, RNA, proteins and enzymes to develop new therapeutics and diagnostics. Two main biotechnologies in health are: (a) Biotechnology therapies and (b) Bioinformatics and diagnostics (source: Report – Human health biotechnologies to 2015). The scope of this effort would include the following key attributes: Drivers to change, technology and research, government policies and regulation, health care delivery systems, stakeholders, global economies, demographics and human resources, climate changes, security, and the interaction of animal and human health drivers. (Source: OECD International Futures Project on "The Bioeconomy to 2030: Designing a Policy Agenda - Health Biotechnology to 2030)

Recommended Action #2a: Increase the emphasis on interdisciplinary research that fuels the bioeconomy by accelerating the discovery, innovation, and application of nanoscale properties that catalyze high impact market opportunities.

12/09/11: Dennis LaJeunesse, [redacted] Associate Professor, Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment 2b: On the biomimetic development of novel "green" textile and composite materials, using nanobiotechnology

The natural world is filled with biologically significant composite materials that are biocompatible, sustainable, and diverse in organization and utility.

Recommended Action 2b: Discover, understand, and develop new technology to identify and implement novel textile and composite materials, with designed and useful functionality. For example, biomimetic approaches fabricating and manipulating nanofibers, such as those based on chitin and cellulose, could enable a revolution in sustainable, highly selective, and low energy nanomanufacturing.

12/09/11: Daniel J.C. Herr, [redacted] Chair - Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment 2c: On high risk, high impact bioeconomic opportunities

Nature offers a hierarchy of approaches to patterning structures. At one end of the spectrum, erosion and top down sculpting approaches to fabrication are examples of processes that depend on external forces, such as wind water, and light that subtractively remove material to create structures. At the other end of the fabrication hierarchy, the programmed assembly of living systems represents a bottoms-up approach that leverages the rich information contained within the material building blocks that assembly into useful nanostructures that maintain and replicate living systems. Research in nanomanufacturing will be a key driver for a sustainable bio-economy. However, the lag time for revolutionary high impact concepts to impact and benefit society is typically thirty years (See D. Herr's and V. Zhirnov's study on the discovery and innovation cycle.) These long discovery and innovation lead times for breakthrough technologies require strategic and sustained support. Potential high impact R&D breakthroughs in the next 20 years include:

- Biomimetic and deterministic design and low energy nanomanufactuing of high performance, functional materials, such as by directed self-assembly.
- Systems that are powered from ambient biological temperatures and leverage bioenergetic materials and processes, such as ATP and photosynthesis.
- Self-adapting and self-healing materials and fabrication methods.
- Distributed intelligent networks of autonomous systems, composed at the nano-level, with adaptive emergent behaviors, such as a synthetic neutrophil.

Recommended Action #2c: Develop mechanisms for providing strategic and sustained support, i.e. 15-20 years, for high impact, high risk research that enables a robust bioeconomy.

Recommended Action #2d: Support research that develops a foundational understanding of the language of materials and biomimetic assembly processes. This knowledgebase will enable us to leverage emergent nanoscopic processes to facilitate the fabrication of useful and functional nanostructures, nanodevices, and integrated nanosystems.

(3) What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry

could rally behind (e.g., NIH $1,000 genome initiative \http://www.genome.gov/27541190\)?

12/09/11: Daniel J.C. Herr, [redacted] Chair - Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #3: On nanomaterials and nanofabrication trends that would accelerate the emergence of a bioeconomy

There is a trend towards biomimetically designed materials that express desired structure and function. For example, directed self-assembly, which exhibits potential for forming sub-10 nm structures in desired and useful patterns, is emerging as an alternative to traditional photoresist-based pattern transfer processes. Eventually, these self-assembling materials may incorporate other useful functionality, such as insulating, semiconducting, conducting, sensing, and/or energy harvesting properties, which will obviate the need for certain etch processes. This biomimetic approach would facilitate the trend towards green and sustainable, high performance chemistries and low energy processes.

Additionally, for emerging More-than-Moore technologies, where scaling is less important, there is a tremendous need for designing and synthesizing functional materials in adjacent spaces, to the nanoelectronics domain, such as energy and bioelectronics, which can be integrated onto a CMOS platform. With respect to bioelectronics, the highest priority emergent needs include personalized medical diagnostics and monitoring, implantable devices and prosthetics, and biocompatible imaging systems. In the areas of implantable devices and prosthetics, there is a tremendous research need for understanding and engineering a robust biotic-abiotic nanointerface, which does not biofoul over time.

Innovations in carbon based electronics, i.e. carbon nanotubes and graphene based devices, require a significant amount of fundamental chemistry to understand their growth mechanisms and dynamics and their interactions with other matter. For carbon nanotubes [CNTs], the 'holy grail' has been to grow them with controlled dimensions, chirality, and functional properties. We are on the verge of developing strategies for achieving this level of control in CNT synthesis. For graphene systems, we are much lower on the learning curve, and a significant level of foundational work is needed before these can be considered for manufacturing.

Deterministic fabrication may be considered an extension of nanoengineered patterning, as it may leverage top down, hybrid, or bottom up approaches. As devices continue to scale, fewer dopant atoms are needed in the channel region. Soon, the number of required dopant atoms will correspond to a small number, say around 100 atoms. At this point, any variation in dopant count and position will adversely impact device performance and performance uniformity. Hence, there is a trend towards fully depleted devices, for which there are no dopant atoms in the channel region. However, even in this scenario, any variation at the interfaces between the channel and the source, drain, and gate stack will induce variations in device performance. Ultimately, more deterministic approaches to

nanofabrication will be needed to achieve the required levels of performance and uniformity. As a proof of principle, biological systems have mastered the ability to grow precise replicates of complex functional structures.

Recommended Action #3: Support and accelerate the creation of a predictive nano- and bio-materials by design infrastructure, with integrated experimental, nano-measurement, and theoretical tool development. Simulation tools are needed to predict and assess trade-offs between material manufacturability, functional performance, cost, and sustainability. However, a considerable amount of 'dotting-the-I' type research will be needed to develop the required materials database. High impact Science and Nature type papers work against this strategic need. I see very little national support for funding this type of work. The nanomaterial genomics initiative represents a first step towards achieving this goal.

(4) The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

Moving life sciences breakthroughs from lab to market: It is a challenge to commercialize advances in the life sciences because of the risk, expense, and need for many years of sustained investment. The Administration is interested in steps that it can take directly, but is also interested in encouraging experimentation with new private-sector-led models for funding commercialization of life sciences research.

(5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

12/09/11: James G. Ryan, [redacted] Founding Dean, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #5a: On Nanomanufacturing at the Joint School of Nanoscience and Nanoengineering

The bold vision to develop a joint graduate school required that the universities look beyond traditional academic models and the national goal of maintaining competitiveness in the manufacturing sector requires that we as a nation look beyond traditional models. [See attached document white paper entitled, "**Nanomanufacturing at the Joint School of Nanoscience and Nanoengineering".]**

Recommended Action 5a: We must develop and build "aggressively interdisciplinary" models that integrate education, research, and public-private partnerships to enable innovative manufacturing technologies. Technologies alone are not enough. We also need to promote methods of commercialization that take ideas from the lab to the factory floor in more efficient ways to assure leadership in advanced manufacturing. Key factors include innovative approaches for: Educational outreach and workforce training, nanomanufacturing science and technology research, and improved commercialization, through effective public-private partnerships that collaboratively leverages the expertise of key stakeholders.

12/09/11: Daniel J.C. Herr, [redacted] Chair - Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #5b: On policy barriers to achieving a bioeconomy

In 1996, Semiconductor Research Corporation and the National Science Foundation launched a joint Engineering Research Center for Environmentally Benign Semiconductor Manufacturing. The process for selecting and managing this center addressed the core needs of the key stakeholders, especially with respect to conflict of interest concerns. While jointly funded by SRC and NSF, this ERC served as a flagship program and a best practice for true public-private partnership. The Focus Center Research Program and the Nanoelectronics Research Initiative represent additional examples of successful and highly valued SRC public-private partnerships [PPP] with DARPA and NIST, respectively.

In the bioelectronics arena, there appears to be a policy barrier that prevents NIH and industry from developing a true strategic research partnership, which seems to be based on a perceived concern for potential conflicts of interest. Currently, the NIH foundation can accept money from an industrial 'partner'. However, it is my understanding that NIH will not engage these 'partners' in defining the call for proposals, selecting the projects to be funded, or assessing the progress of the funded research. In this model, the partnership consists of industry throwing money over the fence. Unfortunately, this approach presents a barrier to leveraging the expertise of each stakeholder and to exploring true convergent opportunities between government, academic, and industrial sectors. For example, the direct collaboration between the biotechnology and nanoelectronics communities could open new markets, create significant job opportunities, and revolutionize the delivery of health care, while avoiding conflicts of interest and maintaining appropriate transparency.

Recommended Action #5b: Develop a set of best practices for successful and effective public-private partnerships between government funding agencies and strategic industrial sectors. A simple, standard, and open process for government and industry to work together as partners would catalyze innovation, drive biological discovery research into the market, and create jobs for the bioeconomy.

12/09/11: Christopher Kepley, [redacted] Associate Professor, Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #5c: On barriers to and opportunities for transitioning biological research discoveries from labs to commercial markets?
A key barrier is the lack of support for the tidal wave of novel, proof-of-principal nanotechnology-based diagnostic, therapeutic, and theranostic systems emerging in academic and government labs. In some cases, perceived toxicity concerns, based on little data, can block a novel and meritorious technology from receiving the critical support needed to realize its potential and address key health challenges.

Recommended Action #5c: Consider developing vehicles for accelerating the investment in and assessment of high risk options that exhibit high potential impact and benefits, while maintaining appropriate checks and balances to protect public health.

(6) What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs \http://www.sbir.gov/\ would help accelerate commercialization of federally-funded bioeconomy-related research?

(7) What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

(8) What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

Workforce development: Investment in education and training is essential to creating a technically-skilled 21st century American bioeconomy workforce.

(9) The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

12/09/11: Daniel J.C. Herr, [redacted] Chair - Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #9: On preparing and sustaining scientists and engineers for private sector bioeconomy jobs.

Recommended Action #9a: Integrate entrepreneurship training programs within graduate level curricula

Recommended Action #9b: Bring continuing educational programs to the workers, such as through on-line Professional Masters Programs. This will make it easier for private sector scientists and engineers to remain current and adapt to a dynamic bioeconomy.

(10) What roles should community colleges play in training the bioeconomy workforce of the future?

(11) What role should the private sector play in training future bioeconomy scientists and engineers?

(12) What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

12/09/11: Daniel J.C. Herr, [redacted] Chair - Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #12: On encouraging successful entrepreneurship

Recommended Action #12: Provide seed corn support for SBIR-like graduate level professional development classes, for developing and exercising entrepreneurial skills in faculty, graduate students, and postdocs.

Reducing regulatory barriers to the bioeconomy: As President Obama has stated, our regulatory system must ``identify and use the best, most innovative, and least burdensome tools for achieving regulatory ends'' and ``protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation.''

(13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

12/09/11: Ethan Will Taylor, [redacted] Senior Research Professor, Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment 13a: On reducing regulatory barriers

For nanobiobiotechnology and related areas such as "Synthetic Biology" to reach their full potential, which I believe is vast, there will have to be a concerted effort to avoid the accumulation of crippling regulations based upon earlier stages of the science, when the fear of the unknown can lead to regulations airing on the side of great caution.

Specifically, as chairman of the UNCG IBC, and having seen what goes down here as a microcosm of other institutions, I am thinking of regulatory procedures surrounding the use of recombinant DNA. These date back to the mid-1970s when DNA splicing and cloning were first invented, and there was great fear that the technology could lead to the creation of "chimeras": literal monsters that could wreak great havoc on the planet when unleashed, very similar to some of the current fears that we've heard about nanotechnology.

As the decades have gone by, recombinant DNA and cloning have become ubiquitous, and commercialized in a vast number of available cloning vectors, bioassay kits, etc., and we are even seeing the emergence of a synthetic biology “hacker” home/garage lab movement, as recently reported in Wired magazine. It is now understood that the original fears from the 1970s that shaped the regulatory environment were substantially overblown, and a very large amount of work that is done in this area is routine to the point of boredom, often having been taken over by companies, which perform many of the services up to and including the creation of complex expression vectors optimized for your organism of choice, and even high school students are now trained in basic DNA manipulations in more progressive locations.

Yet in the academic environment in particular, any institution which aspires to get NIH grant funding has to have an “Institutional Biosafety Committee”, which is charged to review all novel recombinant DNA experiments and constructs prior to their implementation. The same committee deals with review of the use of biohazardous organisms, leading to a further association between the idea of biological hazard and manipulations of DNA.

Despite the creation of certain "exempt" categories, which nonetheless required disclosures on protocol forms and some sort of streamlined committee approval, if the full rigor of the intended process were to be applied, a needless amount of disclosure and review, and inhibition of fully creative experimentation, would descend upon labs across the country. In reality, in many cases a minimal nod to the regulatory process is given, only a subset of experiments are documented, and novel manipulations proceed despite this process. I would venture to speculate that in a majority of research institutions, a substantial percentage of recombinant DNA and synthetic biology research, routine and otherwise, is probably going on in technical violation of the disclosure and protocol review process. Pressure on institutions to attain more compliance by research faculty may lead to more protocols being disclosed, but may also lead to a dampening of the creative spirit. An atmosphere of excessive regulation inevitably leads to those regulations being flouted, accompanied by disrespect for regulations in general, which is undesirable in organizations and in societies.

The fact is, the fundamental building blocks of biochemistry have been perfected over several billion years of evolutionary time, and provide us with tools and prototypical self-assembling nanomachines of astonishing efficiency and diversity, from which there is the potential to engineer new types of hybrid devices based upon a biomimetic concept, such as that applied in the "BioBricks" approach to synthetic biology. We will have no choice but

to learn to use these tools in the most creative ways possible, if we are to maintain a global competitive edge.

The current regulatory environment could be compared to a situation in which engineers with a collection of screws, nuts, bolts, metal beams, rods, motors and an entire collection of building blocks, were told they could not create any new device with these components unless the design was submitted for approval by a committee of experts. Within their set of materials and tools, there may exist hazardous components; such as razor blades, high-voltage devices, toxic adhesive solvents, etc. It is reasonable to expect guidelines for the use of these particularly hazardous tools and materials. But to expect to regulate and review, in advance, the designs for every prototype and novel concept for electromechanical machines, even as those designs are being tried out and modified during optimization of an invention, would be unreasonable.

Recommended Action #13a: Define a large subset of the biological building blocks as fundamentally low risk, focus on particularly hazardous components such as specific genes for toxins and pathogenic mechanisms, and simplify the regulatory process so that practitioners of creative synthetic biology, in the broadest sense, will not be required to justify and wait for committee approval for every new idea for every new experiment they devise.

12/09/11: Marinella Sandros, [redacted] Assistant Professor, Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina 27402

Comment #13b: On reducing regulatory barriers
What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

The biggest barrier is limited access for academic scientists to collaborate with industrial companies, due to IP issues. I think having a non-profit private entity that can bridge academia and industry together will overcome these issues.

Recommended Action #13b: I believe if the government can modify some of the restrictions on how tax dollars can be used, I think we can encourage [collaboration, innovation, and job creation] as we are trying to do at JSNN. I believe that there are few models like this in the US. I truly believe if we can have closer relationships with industry we can move biological innovations much quicker to commercial markets...

(14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

(15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

Public-private partnerships: The Administration is interested in serving as a catalyst for public-private partnerships that build the bioeconomy and address important unmet needs in areas such as health, energy, agriculture, and environment.

(16) What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

12/09/11: Daniel J.C. Herr, [redacted] Chair - Department of Nanoscience, Joint School of Nanoscience and Nanoengineering, Greensboro, North Carolina

Comment #16: On Public-Private Partnerships: Highest impact opportunities and processes

The highest impact PPP opportunities for the bioeconomy are:

1. Personalized medical devices and monitoring
2. Prosthetics and implantable devices
3. Bioimaging, i.e. from in vivo-intracellular imaging to high resolution, high throughput full body scans.

[For more information, please see the reports from Semiconductor Research Corporation's two recent Bioelectronics Roundtables that focused on prioritizing win-win bioelectronics opportunities between the biotechnology and nanoelectronics communities within government, academia, and industry.]

Recommended Action #16: Regarding "What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership", please see Daniel Herr's comments and recommendation for Question #5, above.

(17) What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

Please contact any of the contributors listed above, if you have any questions or would like additional information.

Compiled and edited by Daniel J.C. Herr, [redacted]
Submitted: December 11, 2011

Nanomanufacturing at the Joint School of Nanoscience and Nanoengineering:

A White Paper submitted to the Advanced Manufacturing Partnership Steering Committee

James G. Ryan, Ph.D.

Founding Dean

Joint School of Nanoscience and Nanoengineering

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8/23/11

Background

The Joint School of Nanoscience and Nanoengineering (JSNN) is a collaboration of North Carolina A&T State University (NC A&T SU) and The University of North Carolina at Greensboro (UNCG). NC A&T SU is an Historically Black University with strong programs in the basic sciences and engineering. UNCG, the former Woman's College of the UNC system, has a strong tradition in the liberal arts and has built considerable capabilities in the basic sciences. NC A&T SU and UNCG have come together to create this new joint school in order to reach far beyond what either could have achieved alone. The core values of JSNN include collaboration, innovation and cooperative, technology-driven problem solving. JSNN is one of only two schools in the U.S. to have both nanoscience and nanoengineering degree programs. Although NC A&T SU awards the Nanoengineering degrees and UNCG awards the Nanoscience degrees, the joint nature of the school enables students to take classes from both universities and gain a true interdisciplinary perspective. The bold vision to develop a joint graduate school required that the universities look beyond traditional academic models and the national goal of maintaining competitiveness in the manufacturing sector requires that we as a nation look beyond traditional models. We must develop and build "aggressively interdisciplinary" models that integrate education, research, and public-private partnerships to enable innovative manufacturing technologies. Technologies alone are not enough. We also need to promote methods of commercialization that take ideas from the lab to the factory floor in more efficient ways to assure leadership in advanced manufacturing.

Proposal

The United States is a leader in the development of nanotechnologies of all kinds, but due to the enabling aspects of nanotechnology, many countries have entered the race to develop new "nano" products and applications. Nanotechnologies are integral to industries critical for national defense, energy independence, health care and economic development. Many "nano" products and applications are plagued by limited volumes and high costs caused by nanomanufacturing difficulties. Leadership in nanomanufacturing will determine leadership in many business sectors in the coming years and is a critical enabler for national priorities such as defense. In order to build an integrated program that assures leadership, a multi-pronged approach must be developed to build a foundation for nanomanufacturing featuring workforce training, manufacturing science and technology research, and improved commercialization approaches through public-private partnering models. Many U.S. manufacturing companies see their foreign competitors enabled by their governments and although true partnerships between Academia, Government and Industry are difficult to achieve, U.S. nanomanufacturing entities will need the leverage provided by such partnerships in order to implement innovative ideas.

Workforce Training

Workforce training begins with outreach to high schools and particularly with the teachers. It is important that teachers and guidance counselors understand the career options in fields like nanomanufacturing. In order to address these issues, JSNN has provided Guilford County high school science teachers with "nano-training" through our K - 12 outreach programs

with a goal of producing students who will be able to make more informed choices regarding careers and degree options.

Formal workforce training in aspects of nanomanufacturing should take place in Associate, Bachelor's and Graduate degree level programs. Typically, community colleges already focus on workforce training for technician level personnel, often in collaboration with local employers. What is lacking is direct experience with leading-edge technologies requiring extensive infrastructure. JSNN has initiated co-op programs with Guilford Technical Community College and Forsyth Technical Community College employing community college students at JSNN so that they gain hands-on experience with leading-edge infrastructure and equipment

Graduate level education in "nano" at universities is primarily directed at producing R&D personnel. JSNN trains research personnel (through its Ph.D. programs) as well as nanomanufacturing personnel (through its Professional Master of Science in Nanoscience degree program). The Professional Master's program involves Nanoscience and Business courses combined with an internship in order to produce graduates who could work in nanomanufacturing or other fields where a combined science and business background is needed.

Currently, the missing element in JSNN's workforce training strategy is at the Bachelor's degree level. Expertise at JSNN's parent institutions combined with JSNN's "nano" competency could produce unique undergraduate curricula emphasizing nanomanufacturing. For example, a collaboration between JSNN and UNCG's Bryan School of Business could develop a B. S. in Nanomanufacturing Science degree program. Philosophically, it would be patterned after the existing Professional Master of Science in Nanoscience and would combine undergraduate science (emphasizing either Physics, Chemistry, or Biology) and business classes (emphasizing subjects such as Finance, Logistics, Entrpreneurship, Manufacturing Operations, etc.). It is anticipated that the degree program would approach the number of credits for a double major. At NC A&T SU, the School of Technology has initiated discussions with JSNN on a Bachelor's in Nanomanufacturing Technology. This degree would contain undergraduate nanoengineering courses such as Nanomaterials and Principles of Nanoengineering in a curriculum with Engineering Technology courses emphasizing critical elements in building nanomanufacturing capabilities including facilities, equipment, nanomaterials safety and nanodevice operation. The total credits in the Nanomanufacturing Technology major would also be similar to a double major in engineering and technology. These undergraduate programs could also serve as feeder programs for JSNN's advanced degree programs.

Initial funding for expansion of the community college co-op program and undergraduate curriculum planning would be approximately $100K. The ongoing operating expenses of the programs (including hiring one additional faculty in each department to teach in the program and three staff to coordinate program operations) would be ~$900K/year*.

Nanomanufacturing Science and Technology Research

The unique environment of the JSNN serves as a “reactor” for emerging technologies and fosters an environment conducive to discovery. Research underway at JSNN focuses on real-world problems and includes development of new drug delivery methods, nanobioelectronic devices to diagnose traumatic brain injury and nanocomposite technologies that create lighter, stronger materials for the automotive, aircraft and energy sectors.

At JSNN, innovation is encouraged in all areas and we work to make sure that the innovative spirit permeates the organization. Innovation involves (in roughly equal parts)

understanding what the key problems are in critical fields, having a team of bright, action-oriented problem solvers who learn from every observation and a culture that encourages not only invention, but also innovation and openness. The problem set and professional team exist in most advanced research facilities, but the culture that encourages people to create solutions to problems (invention) and to take invention to the next step where products and (potentially) wealth are created (innovation) along with a willingness to discuss ideas within the team (openness) is rare. At JSNN we are attempting to build this type of culture through an informal weekly “Inventions and Innovations” meeting where faculty, staff, students, and partners can attend to discuss new ideas. Also, we work to actively extract innovations from research results. Moving the ideas from the labs to factory floors is part of JSNN's partnership strategy (see below).

JSNN's current nanomanufacturing research plan includes three Nanoscience topics and three Nanoengineering topics. The Nanoscience areas include Nanoparticle Manufacturing methods, Nanopore Fabrication and Nanobiomanufacturing . Nanoparticles are included in a variety of products from cosmetics to fighter jets. This broad group of materials includes fullerenes, nanotubes, self-assembled structures, thin films and many others. It is difficult to make the most technologically useful particles in large quantities. For example, fullerene materials find applications in pharmaceutical, defense and structural applications although only lab-scale volumes are available. Nanopore Fabrication is a comparatively new area and has seen genomic research applications, but with recent breakthroughs at JSNN, we believe nanopores will be useful in a variety of purification applications as well. Methods used to form nanopores are relatively slow and productivity improvements are needed before they can be evaluated for large scale applications (e.g. separating and purifying nanoparticles). Improved nanobiomanufacturing techniques are needed for biomolecules used in medical diagnostic and other sensors, chromatographic separation technology and biomedical applications.

The Nanoengineering topics include Nanocomposite Materials Fabrication, Nanobioelectronics and Computational Nanotechnology. Nanocomposites involve the use of nanofibers in combination with conventional materials (e.g. fiberglass, carbon fiber, etc.). Nanocomposite materials may be used in aerospace, wind energy and battery applications. Nanofibers are often made by a technique called electrospinning. Although commercial electrospinning equipment is available, it works well for polymers and some inorganic fibers but is not useful for certain glass and advanced inorganic composition nanofibers. New equipment technology is needed for high productivity electrospinning of TEOS-based glass nanofibers and nanofibers based on materials such as boron nitride (BN). Both TEOS-based glass and BN nanofibers are of great interest to DoD. Nanobioelectronics combines computer chip technology with biotechnology in order to create new diagnostic or medical devices. In general, most industrial cleanrooms are not constructed to be capable of working with biomolecules or bacteria incorporated into the circuitry. New protocols for combined Nano and Bio manufacturing must be developed (JSNN has a cleanroom capable of both nano and bio technologies). Computational Nanotechnology will also be investigated to develop new predictive models for "nanobio" problems.

Although each of these topics is connected to national priorities, two in particular are critical to the Air Force (and DoD in general); Nanoparticle Manufacturing and Nanocomposite Materials Fabrication. JSNN plans to devote significant laboratory facilities to Nanoparticle Manufacturing technologies including the Nanoparticle Synthesis and Nanoparticle Characterization laboratories as well as a portion of the Nanochemistry laboratory. JSNN plans

to work with AxNano, Inc. to develop new nanoparticle fabrication and purification methods (see Partnership section below). JSNN's Nanocomposite Fabrication Laboratory combined with the assets in the Nanocomposite Scale-up and Commercialization Laboratory (jointly used by JSNN's partner Advaero Technologies, Inc.) will be used to promote improvements in Nanocomposite Fabrication Technology. In addition, portions of seven other laboratories in JSNN's state-of-the-art facility will be utilized in the nanomanufacturing research effort including its 7000 square foot cleanroom, visualization center, and its extensive characterization and metrology laboratories.

JSNN plans to support this research from its North Carolina state recurring budget and research grants obtained from a variety of sources. These programs can be enhanced and extended with additional federal funding, but if the goal is true acceleration of nanomanufacturing then an infrastructure created for the specific purpose is needed. We propose construction of a 60,000 square foot National Nanomanufacturing Center (NNC) (~$20 Million + ~$2 Million per year of operating funds*) on the Gateway South Campus in Greensboro, NC. The facility would be optimized for prototyping and would enable the integrated nanomanufacturing program of workforce training, manufacturing research and improved commercialization though industrial partnerships.

The facility would contain classrooms and distance learning capabilities in order to reach all interested parties. The research labs would be constructed as large prototyping facilities. The Nanoparticle Manufacturing facility would contain particle synthesis equipment and specialized hoods with appropriate chemical handling, piping and facilities to perform continuous flow separations and extractions. JSNN's Nanopore Fabrication technology might also provide critical capabilities for this effort. JSNN's future partner AxNano, Inc. will work with JSNN personnel to develop high yield, high productivity Nanoparticle Manufacturing methods. The Nanocomposite Fabrication facility will be large enough to permit composite lay-up and testing of large objects such as aircraft parts and windmill blades and still have a portion dedicated to the development of high productivity electrospinning equipment for nanofiber fabrication and automated equipment to fabricate structures containing delicate nanomaterials. JSNN's partner Advaero Technologies will work with the faculty in this space. JSNN's other nanocomposite partners will also be able to gain leverage using this space. Other nanomanufacturing projects would also have prototyping capability in the NNC but will require less space than the Nanoparticle and Nanocomposite thrusts. Facilities such as the proposed NNC have a way of galvanizing attention, attracting corporations and enabling innovation. For example, facilities such as Clemson University's Research Campus have provided significant advantage to the automotive companies in South Carolina and UAlbany's Albany Nanotech has become a center of innovation for the semiconductor industry. The NNC would be able to produce prototypes and focus on commercializing innovation while leveraging JSNN's nearby scientific capabilities for analysis, materials testing and characterization, modeling and specialty syntheses.

Improved commercialization approaches through public-private partnering models

JSNN is located on the Gateway University Research Park (Gateway) South Campus. Gateway is also a collaborative initiative of NC A&T SU and UNCG and is responsible for building and tooling the $64.3M JSNN facility using funding from the North Carolina General Assembly. Together, JSNN and Gateway work to attract industrial partners, with JSNN offering leading-edge education and research programs and Gateway offering advanced facilities to

support new ventures with commercial partners. Shared infrastructure is critical for collaboration. Universities, governments and industries have different business models but all need the same scientific/engineering infrastructure to be successful. JSNN and Gateway (as with any successful burden sharing organization) strive to enable each participant to get what they need from the common infrastructure.

JSNN's partners are a combination of start-up and well-established companies. Partners or potential partners for each of the nanomanufacturing thrusts are shown below in parenthesis. JSNN has either completed contracts or entered negotiations with each entity.

- Nanoparticle Manufacturing (AxNano, Inc.)
- Nanopore Fabrication (Carl Zeiss SMT)
- Biomanufacturing Techniques (Horiba)
- Nanocomposites for Wind energy (Advaero Technologies, Xanofi)
- Nanobioelectronics (MEMSCAP)
- Computational Nanotechnology (TBD)

Gateway and JSNN have also developed collaborations with companies such as RF Micro Devices and Agilent Technologies and are currently pursuing potential partnership opportunities with over twenty high technology firms. Although access to facilities is an attraction for companies, the biggest attractive force often involves equipment. In order to attract large entities with complex nanomanufacturing problems, a budget for investment in equipment must be developed. In order for the NNC to attract partners, ~$2 Million per year* would be requested to purchase equipment. The costs of a proposed partnership program are identified before an agreement is executed including labor, consumables, maintenance and capital equipment. As a general rule, total program costs are equally divided but in our model, Gateway would own and maintain the equipment and make it available to all partners.

To date, JSNN/Gateway co-location model has created 192 jobs at an average salary over of $70,000. The economic impact of the JSNN/Gateway model on the Piedmont Triad region is conservatively projected to be approximately one-half billion dollars over a ten year period but more needs to be done to build a strong 21st century manufacturing-oriented economy. The NNC will initially create numerous construction jobs, but more importantly, it will create more than 200 nanomanufacturing R&D jobs on the Gateway campus and more than 500 jobs in the Piedmont Triad as well as provide a prolific job creation engine for the knowledge-based nanomanufacturing sector so critical for American competitiveness.

* Proposed funding amounts are estimates intended to show approximate "opportunity cost". More detailed proposals with detailed budgets would be developed upon request.

December 20, 2011

The Honorable John P. Holdren, Ph.D.
Assistant to the President for Science and Technology, and
Director, Office of Science and Technology Policy
The White House
bioeconomy@ostp.gov

Re: Office of Science and Technology Policy. Request for Information: Building a 21st Century Bioeconomy. [Docket No. 2011–26088] 76 FR 62869. October 11, 2011.

Dear Dr. Holdren:

CropLife America (CLA) is pleased to provide comments to the Office of Science and Technology Policy regarding building the 21st century Bioeconomy. CLA represent the companies that develop, manufacture, formulate and distribute crop protection chemicals and plant science solutions for agriculture and pest management, including products used as and in conjunction with plant incorporated protectants. CLA member companies produce, sell and distribute virtually all the crop protection and biotechnology products used by American producers. CLA and its predecessor organizations recently celebrated a 75th anniversary.

CLA lauds the development of a National Bioeconomy Blueprint to move ideas from the lab to market and detail the Administration-wide steps to harness biological research innovations to address national challenges in health, food, energy, and the environment while creating high-wage high-skill jobs. We agree that biological research lays the foundation of a significant portion of our economy, especially agricultural and modern farming production. By better leveraging our national investments in biological research and development, the Administration will grow the jobs of the future and improve the lives of all Americans. We hope that the Blueprint is successful in focusing on reforms to speed up commercialization and open new markets, strategic R&D investments to accelerate innovation, regulatory reforms to reduce unnecessary burdens on innovators, enhanced workforce training to develop the next generation of scientists and engineers, and the development of public-private partnerships.

Global Challenges Require Robust R&D-To-Market Strategies

The crop protection industry is committed to helping farmers produce an affordable and sustainable supply of food to help feed a hungry world and modern agricultural research is vital to this effort.

- Globally, over 900 million people - one-sixth of the world population - suffer from malnutrition. Agricultural output *has to double in the next 20-30 years* in order to feed the world's population, which the United Nations predicts will grow by 1.7 billion more people by 2030. To meet the global challenges of food production and security, high-yield production of biotech crops using crop protection products will continue as the primary agricultural practices.

- The early adoption of crop protection products and the recent rapid adoption of biotech crops have advanced modern agriculture through use of no/reduced tillage production systems and integrated pest management. These approaches provide both economic and environmental benefits including reduced soil erosion and improved soil moisture levels.

- The crop protection industry makes a significant investment in research and development. Intensive scientific research and robust investment in technology during the past 50 years helped farmers double food production with out a change in the footprint of total cultivated farmland. Crop protection is one of the most research-intensive industries in existence, with companies investing about 12% of their turnover in research and development (R&D). The top 10 plant science companies invest an estimated $3.75 billion in R&D per year to discover, conduct tests to ensure safety and develop new products.

    - Industry estimates that average research and development costs for one new crop protection product to reach commercialization are $256 million (a 40% increase in the U.S. and Europe over the past decade), and that the process takes an average of ten years (CLA and European Crop Protection Association, 2010. The Cost of New Agrochemical Product Discovery, Development and Registration in 1995, 2000 and 2005-2008. R&D Expenditure in 2007 and expectations for 2010. Final Report, January 2010).

- The rigorous science-based regulation of crop protection and agricultural biotechnology serves as the foundation for the safe use of these technologies. These regulatory processes, and subsequent policies, must continue to be grounded in science if we are to approve new products and advance modern agriculture.

Regulatory Reform is Needed in Crop Protection

CLA has addressed U.S. Environmental Protection Agency regulatory reform separately in comments specific to pesticide registration and submitted to Docket No. EPA-HQOA-2011-0156. In the same docket, CLA was also party to comments from the chemical industry submitted from a coalition led by the American Chemistry Council which addressed several important general regulatory issues. CLA is also a member of the Endocrine Policy Forum, which has submitted more detailed comments to EPA-HQOA-2011-0156 with special relevance to EPA's Endocrine Disruptor Screening Program.

CLA urges reform of several pesticide regulations to stimulate lab-to-market for the benefit of agriculture and the crop protection industry. Each of the following regulatory issues is evidence of duplicative regulation, and wasteful use of government resources. Further, these proposed regulations provide NO additional environmental protection.

1. The permitting plan for aquatic pesticide use, proposed by EPA's Office of Water under the National Pollutant Discharge Elimination System (NPDES) and subject to the Clean Water Act, is duplicative of the registration process for pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

2. The Endangered Species Act (ESA) consultation process for pesticides conducted by the National Marine Fisheries Service and the U.S. Fish and Wildlife Service is also largely duplicative of the registration process for pesticides under FIFRA.

3. The Federal Food, Drug and Cosmetic Act (FFDCA) §408(i):"Data and information that are or have been submitted to the Administrator under this section ... in support of a tolerance or an exemption from a tolerance shall be entitled to confidential treatment for reasons of business confidentiality and *to exclusive use and data compensation* to the same extent provided by sections 3 and 10 of the Federal Insecticide, Fungicide, and Rodenticide Act." (Emphasis added.) This provision, enacted as part of the Food Quality Protection Act (FQPA) of 1996, was primarily intended to provide intellectual property protection for data specifically required under FQPA to support inert ingredients in pesticide products. Lacking implementing regulations, the procedures for protecting such data are still uncertain and unclear, leaving registrants without adequate means of assuring they are complying with the law. 4. 40 CFR Part 180 contains voluminous information on the specific tolerances and tolerance exemptions for individual pesticide chemicals on the various food and feed commodities. The rules codified here are frequently modified, added to, and updated. Reformatting the information could make it much more useful and usable for stakeholders.

4. EPA's Integrated Risk Information System covers pesticide active ingredients, along with other chemicals. With respect to pesticides, the work it encompasses and the information included are largely duplicative of what the Office of Pesticide Programs accomplishes in the course of regulating pesticides.

5. All Pesticide Registration (PR) notices should be evaluated to determine which remain in effect; which need changes, updating, or replacement; and which should really be

codified as rules in the Code of Federal Regulations. Some specific examples, including proposed PR notices that have not been finalized:
a. Spray drift
b. Prohibited words and product names on pesticide labels
c. Reporting of nanomaterials in pesticide products

6. Standard Operating Procedures for review of pesticide registration applications (across the range of PRIA categories, and more) need to be established and improved. Standardize how the applications are handled, so EPA reviewers know what to do, and can handle applications consistently and more efficiently. Make the SOPs transparent to registrants so they can prepare better and submit more complete and accurate applications. Encourage better, more frequent, more consistent communication between reviewers and applicants. Do not leave the bureaucratic process and decision making to the whims and capriciousness of individual reviewers, without adequate management supervision.

7. Regarding information transfer, there are several improvements to be made:
- Data call-ins are often poorly handled; EPA fails to hold up its side of the obligation (especially timing and decisions), yet yields no leniency to the registrants to make up for the Agency's tardiness and failings, significantly increasing the burden and stress on the registrants.
- Test orders issued under FQPA – need clear rules and procedures for their use, or they should be placed directly under FIFRA data call-in regulations.
- Pesticide registration forms could be improved significantly as a joint project between registrants and regulators.
- Information Collection Requests – greater education of stakeholders about their importance and the opportunity for meaningful input.

8. Regarding procedural clarification, there are several improvements to be made:
- Establish clearer procedures within the Administrative Procedures Act for input to the regulatory process from the variety of internet forums, media, and possibilities. These are being handled too casually and chaotically.
- Clarify the roles and rights of state regulators in EPA regulatory processes, with respect to the Federal Advisory Committee Act, and the corresponding rights and roles of other stakeholders.
- Unnecessary delays in pesticide regulatory decisions made under FIFRA undermine the intellectual property protections that applicants and registrants are afforded under patent statutes and regulations, as well as the exclusive use and data compensation provisions of FIFRA. The delays discourage innovation and penalize innovators.

Regulatory Reform is Needed in Agricultural Biotechnology

CLA urges reform of agricultural biotechnology regulatory processes to stimulate lab-to-market for the benefit of agriculture and industry's technology providers.

1. During the past decade, APHIS has reduced the types of small-scale field trials that may be conducted under 30-day notification procedures, and it more recently proposed to terminate the notification system altogether and require full permits for all field trials. The agency has also required breeders to conduct additional tests to measure things only tangentially related to safety and to include the analyses in petitions for deregulation. Consequently, the length of time it takes for APHIS to approve field trial permits and to grant petitions for non-regulated status has been rising dramatically. These increasing and costly delays are particularly burdensome for small firms with high capital costs and for public sector and non-profit institutions that rely on grants to finance their research. But these delays impact all firms in the industry, and they jeopardize the new product pipeline with significant financial and regulatory uncertainty.

2. Currently, the Plant Protection Act merely requires APHIS to act on petitions for non-regulated status "within a reasonable time," but does not specify a deadline for making decisions. Regulations promulgated by APHIS stipulate that the agency may take up to 120 days to review applications for field trial permits and up to 180 days to review petitions for non-regulated status. However, APHIS frequently exceeds these periods, often taking three or four times as long. Recently, for example, APHIS took approximately 500 days to review each of two field trial permit applications that were eventually granted in 2008 and 2009.

Similarly, APHIS has frequently taken several years to grant deregulated status to new biotech varieties, with recent highs exceeding four years. The average review time for deregulation petitions submitted prior to 2000 was a mere six months, and only five of the 51 deregulations granted in that time period took longer than 8 months. In contrast, the average review time for petitions submitted from 2000 to 2011 was a stunning 20 months, and the review time for five of the last eight deregulations granted exceeded 30 months. Currently, there are a dozen such petitions outstanding that have been awaiting an APHIS decision for two years or longer. Yet, while a number of petitions have been withdrawn by sponsors for a variety of reasons – typically having to do with concerns about the crop's potential for commercial success – APHIS has not once denied a deregulation request. This is a testament to the proven overall safety of new biotech crop varieties.

These concerns are not new, nor are American growers the first to raise them. As long ago as November 2004, at a USDA-sponsored workshop on "Public Research and the Regulatory Review of Small-Market (Specialty) Biotechnology-Derived Crops," several participants expressed their frustration that review times had begun to grow increasingly lengthier beginning around the year 2000. And participants at a January 2007 workshop jointly sponsored by APHIS and the Pew Initiative for Food and Biotechnology agreed that developing a condensed and predictable timeline for APHIS deregulation decisions was essential for "streamlining and fine-tuning the regulatory process." The published summary of the latter workshop proceedings specifically recommended that APHIS

"[k]eep the timeline and process from submission to decision as short as possible. Some urged that the process be limited to one growing season."

If the developers of new biotech crop varieties – whether they are large or small firms, public sector institutions, or non-profit organizations – do not have confidence that their applications will be reviewed and acted upon in a timely manner they will become less likely to make the investments in new products that have kept American farmers highly productive and internationally competitive. If instead, developers are able to secure more rapid approvals in other countries such as Brazil and China, and reach the market first in those countries, American farmers will be put at an increasingly large disadvantage compared with their international competitors. Additionally, global food insecurity threatens our rapidly growing world population.

3. In order to improve the permitting and deregulation process and ensure that APHIS follows its statutory obligation to base decisions on sound science, congress should (1) establish a statutory limit on APHIS review periods with judicial review of failure to meet such review periods and (2) direct the executive branch to update the federal regulatory framework to streamline regulatory review processes.

In May 2011, Rep. Stephen Fincher and two co-sponsors introduced a bill – the Expediting Agriculture Through Science Act (H.R. 2031) – that would establish a 180-day time period during which APHIS must make a determination on petitions for non-regulated status. The bill would provide up to two 30-day extensions, but the petition would be automatically approved if APHIS has not acted on it by the end of the combined, 240-day period. In addition, for any such petition that APHIS denied, the bill would require a "written, clear, and comprehensive" explanation for its rejection.

CLA therefore encourages the congress and the administration to consider legislation like this that establishes a maximum review period for both field trial permit requests and petitions for non-regulated status. One or more specified extensions could be added to accommodate APHIS time constraints in addressing requests and petitions that pose special challenges, as the Fincher bill proposes. But it is essential that the total time allotted for agency review be established in legislation, so APHIS cannot inappropriately drag out its review beyond a reasonable time period. Stakeholders understand that APHIS decisions would need to be legally defensible, and this paper does not recommend legislation that would weaken USDA's legal defensibility of a petition in question.

4. Regarding final petition approval by the Secretary of Agriculture, in order to ensure the allotted review times, CLA recommends creating a meaningful and predictable expectation for applicants. Statutory language should grant automatic approval for any requests or petitions on which the Secretary has not made a determination by the end of the allotted time. The "clock" should begin once the Environmental Assessment is completed by APHIS and the USDA Office of General Counsel determines that deregulation may proceed. In other words, in this phase, this allotted time would be triggered when the petition is awaiting the Secretary of Agriculture's signature of approval for deregulation. In effect, this serves to preserve the scientific integrity of the regulatory review, and would prevent the politicization of a petition deregulation by

discouraging the Office of the Secretary from "sitting on" a petition due to non-scientific, non-risk based considerations.

5. In addition, CLA urges that in order to prevent APHIS from inappropriately denying field trial permit requests or deregulation petitions in a manner intended to circumvent the allotted time periods, legislation should require the agency to provide applicants with a written, clear, and comprehensive explanation for the agency's determination. This explanation should have to provide in substantial detail the agency's scientific rationale for continuing to treat the regulated article as a plant pest.
American agricultural producers, and biotechnology research & development companies alike are deeply concerned by the shaky future of the U.S. as a leader in this innovation. Due to signals from the U.S. government, stakeholders such as these lack the regulatory certainty to continue investing in the U.S. with confidence in its regulatory system.

Agricultural Research Drives Innovation Through a Trained Workforce

CLA urges the Administration to increase the federal funding of food and agricultural research, extension and education and create new opportunities for public-private partnerships. There must be adequate investment in research and training of future agricultural experts to enhance industry lab-to-market approaches. Scientific research forms the cornerstone of modern and safe products that have been registered through a solid, safe, science-based regulatory process. Industry has massive investments in crop protection and agricultural biotechnology research; but public funding is needed as well, to fully leverage research opportunities and provide solutions to growers. Therefore, CLA believes that federal funding for food and agricultural research, extension and education represents a top national priority and a necessary long-term national commitment. In this regard, we agree with the comments submitted to this docket by the National Coalition for Food and Agricultural Research (NCFAR). CLA recognizes that regulatory reform and policies developed today must drive investment and prioritization of research and education, which in turn, stimulates future innovation through new plant and pest biology and crop protection technologies, as well as to train future scientists and employees for agriculture.

In conclusion, modern agriculture must advance based on the use of new technologies in crop protection and agricultural biotechnology. These technologies are hampered by duplicativeness and inefficiencies in regulation--we must strive to access good science through improvements in regulatory processes. Food security through modern agriculture is critical to delivery of human health care, reduction in hunger, and increasing energy supply, all in a sustainable manner with minimal negative impact on the environment. CLA is proud of the long record of success by the science-based crop protection industry which will continue to allow not only American farmers, but consumers world-wide to share in enhanced quality of life and health, through more affordable and sustainable supplies of food, feed, fiber, fuel and industrial products -- benefits and new opportunities offered by modern agriculture.

CLA urges the OSTP to address the limitations in regulation of products in crop protection and agricultural biotechnology. To inhibit advancement from lab-to-market of these technologies, given the current global grand challenges, ignores the current success of modern agriculture and avoids the honest analysis toward solutions for both U.S. and international food security.

Dr. Holdren, CLA offers our assistance to you as the OSTP embarks on development of the Blueprint. Please do not hesitate to contact us as leaders in advocacy of science-based innovation in agriculture. We appreciate the opportunity to comment. If there are questions, please do not hesitate to contact me ([redacted]; [redacted]).

Sincerely,

Barbara P. Glenn, Ph.D.
Vice President
Science & Regulatory Affairs