

Framework for a Successful Bioeconomy



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, glycomics, 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. Biofuel crops should ideally be produced in areas where there is less productive land for feed production. Dual [“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% CO₂, 48% methane and 52% NO -- the latter is 300 times greater than CO₂ 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 finely 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 than 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 glycomics 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 crops 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 in 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, glycomics, 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 downstream 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) 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?

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 (EMA) 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.