Alliance
FOR AGING RESEARCH

www.agingresearch.org

750 17th Street, NW | Suite 1100 | Washington, DC 20006
T 202.293.2856 | F 202.955.8394

December 6, 2011

John .P. Holdren
Director
White House Office of Science and Technology Policy
Executive Office of the President
725 17th Street, Room 5228
Washington, DC 20502

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