



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?