41 Nanoneuroscience and Nanoneurosurgery
A Key Component of President Obama's Brain Mapping Initiative

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INTRODUCTION

President Obama said in his April 2nd speech "We have been a nation of dreamers and risk-takers; people who see what nobody else sees sooner than anybody else sees it. We do innovation better than anybody else—and that makes our economy stronger. When we invest in the best ideas before anybody else does, our businesses and our workers can make the best products and deliver the best services before anybody else." In the same event at the White House he followed up on the promise he made at his presidential state-of-the-union address and authorized $100 million in additional funding for neuroscience, directing it specifically toward brain mapping efforts (Figure 41.1).

This is a great achievement for the brain mapping community, which has developed and defined the field of Brain Mapping as: The study of the anatomy and function of the brain and spinal cord through the use of imaging (including intra-operative, Microscopic, Endoscopic and Multi-Modality

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FIGURE 41.1 President Obama unveiled the Brain Mapping Initiative before 100 top scientists at the East Wing of the White House on Tuesday April 2nd 2013. Chairman of the Board of SBMT and President of Brain Mapping Foundation, Babak Kateb, was amongst the attendees. (Courtesy of Brain Mapping Foundation.)

imaging), Immunohistochemistry, Molecular and optogenetics, Stem cell and Cellular Biology, Engineering (material, electrical and biomedical), Neurophysiology and Nanotechnology.

The Society of Brain Mapping and Therapeutics (SBMT) and the Brain Mapping Foundation (BMF) fully support President Obama's BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies). It is our opinion that before significant funds are committed to speculative technologies, a complete, comprehensive and detailed survey of the key unresolved clinical research questions, and the most promising technologies, should be completed. The initial Brain Activity Mapping (BAM) initiative appeared to be based on a single Neuron article that sketches out a few such technologies, without providing a clear vision about how a BAM could be defined on an organism much more complex than a nematode (*Caenorhabditis elegans*) or fruit fly (*Drosophila*) (Paul Alivisatos et al. 2012a,b). If the ultimate goal is to understand how the human brain works, a more thorough survey of what is known and what can be measured in vivo is required, including all aspects of neuroimaging, nanotechnology, device application, cellular tracking and molecular genomics and photonics (Levy 2013).

Our view is that the nervous system is organized hierarchically over many spatiotemporal time scales, extending from nanometers to meters, and from microseconds to lifetimes. This demands a much more holistic approach to understanding what brain activity is, what it means, and how we can measure it. Organizing a visionary process that lays out critical problems in brain sciences and technical problems at the relevant spatial and temporal scales would serve to improve the quality of this project and prioritize the efficient distribution of limited funds. This could be done in various ways, such as by having high-profile talks and organizing Congresses such as the 10th Annual World

Brain Mapping Congress of the Society for Brain Mapping and Therapeutics (SBMT). This meeting incidentally took place at the Baltimore Convention Center shortly after the President Obama announcement. The meeting brought together more than top 500 scientists from across the globe, including leaders in the field of neuroscience and other relevant disciplines of science and engineering. Such meetings should engage policymakers, physicians and surgeons in order to address neurological disorders from all perspectives (www.WorldBrainMapping.Org).

Clinical input is essential to ensure that knowledge obtained from the BRAIN Initiative is translated into improved health outcomes. Simply mapping brain function and activity is not sufficient. We need to also address the therapeutic aspects of brain mapping to ensure that the knowledge acquired by functional and activity maps actually impacts treatment and healthcare delivery for patients with neurological disorders.

In this final chapter of the textbook we have identified items of relevance to national health issues and tried to address them through 3 major-encompassing programs, which could engage scientists across disciplines and enable translation, integration and commercialization of nanobioelectronics (nanotechnology, stem cell and cellular therapeutics, imaging, and devices). These novel proposed programs are: 1) National Alliance for NanoBioElectonics (NANBE), 2) National Network for Human Brain and Specimen Banks (NNHBSB), and 3) National Data Repository and Analysis for Neuroscience (NDRAN).

PROBLEM TO BE ADDRESSED

Neurologic and psychiatric disorders, including stroke, traumatic brain injury, brain tumors, spinal cord injuries, brain cancers, neurodegenerative disorders (Alzheimer's Disease, Parkinson's Disease, ALS, etc.), developmental disorders, epilepsy and depression, cost the US healthcare system near $400B annually (Rydell and Larson 2012). In order to improve the treatment of these devastating diseases, stimulate relevant research, reduce cost and disabilities, increase productivity and improve rehabilitation, a multidisciplinary approach that mobilizes all assets of the federal government, industry and academia is necessary. If properly designed, this investment in healthcare and research can simultaneously generate jobs and provide the stimulus for solving critical problems in healthcare.

One of the greatest challenges of the early 21st century is the translation and transfer of cutting-edge research and advances made in the nation's diverse research laboratories into the clinical setting. The SBMT and the Brain Mapping Foundation jointly propose the creation of a new Brain Mapping and Therapeutics program within BAMP in order to promote the development of new diagnostic and therapeutic approaches, as well as educational and preventive strategies to preserve and repair brain function. A focused, targeted, goal-oriented effort founded upon interagency and interdisciplinary collaboration can efficiently advance medical technology, fuel job creation (i.e., biotech spinoffs), and foster infrastructure development.

The proposed program would establish novel consortia involving federal agencies, academic centers, private foundations and industry *based on the two congressional initiatives by Congressmen Fattah and Moran*:

> "The Fattah Neuroscience Initiative (FNI) is an innovative, non-incremental policy initiative designed to make major progress in understanding the human brain by intensifying, in a collaborative fashion, federal research efforts across brain disease, disorder, injury, cognition and development. The initiative aims to coordinate Federal research across agencies and draw upon public-private partnerships and the world of academia. The initiative promotes research and discovery across brain cognition, development, disease and injury." and congressman Moran "The Committee encourages the Secretary of Defense to support multi-disciplinary research toward translational medicine that may provide better diagnostic tools and treatment outcomes for service members who suffer from traumatic brain injury, post-traumatic stress disorder, and other neurological diseases. With this support the Secretary of Defense will enable the creation of a nationwide scientific consortium aimed at integrating nanotechnology, stem cell, cellular therapy, medical imaging, electronic medical record, information technology, Brain

Mapping, and medical device. The Committee encourages the Secretary of Defense to provide the capabilities necessary for researchers, scientists, surgeons, physicians, healthcare professionals, and patients to effectively communicate their findings and outcomes. With proper support, translational research outcomes would be augmented through real-time access to information and its integration between researchers, physicians, hospitals, and patients. The Committee encourages the Secretary of Defense to establish this program through the NAVY Bureau of Medicine and Surgery (BUMED). The Committee directs the Secretary of Defense to provide a report not later than 90 days after enactment of this act on a possible implementation of this program."

As opposed to current centers of excellence, the proposed consortia by the Brain Mapping Foundation and Congressman Moran would be: 1) larger and multi-institutional 2) focused upon multiple aspects of a disease, including medical, business, legal, and socioeconomic aspects rather than only single components 3) multifaceted in addressing the impact on overall public health, 4) attentive to job creation in addition to the advancement of science by providing bridge grants for the consortia, which could encourage biotech spinoffs, 5) able to increase investments in the US by encouraging up to 20% investment in the US in the area of Brain Mapping by international partners. These investments could be made by hiring postdocs in the US or by providing other forms of funding based on individual agreements required in the Research Announcement/Agreement. These initiatives are designed to significantly contribute to President Obama's Brain Mapping Initiative through the following key elements of the program, which would include:

The National Alliance for NanoBioElectonics (NANBE) in Brain Mapping

SBMT has developed a global network accessible to all neuroscientists, which could facilitate the translation of basic science and engineering into clinical trials. The National Alliance for NanoBioElectonics (NANBE) could similarly integrate diverse elements including nanotechnology, imaging and diagnostic devices, stem cell and cellular therapies, and genomics in order to develop novel diagnostic and therapeutic innovations that can protect and preserve the brain while simultaneously creating new technologies and new jobs. The NANBE could further foster international partnerships through a global alliance led by the US, which would do even more to create new jobs within the US. This program will be aimed at integration, translation and commercialization of already exciting technologies and treatment modalities and or technologies, which are under development. The alliance will function as a global hub for nanoneuroscisnce, which will help identify the best nanoplatform for imaging, diagnostics and the treatment of neurological disorders (Kateb et al. 2011).

National Network for Human Brain and Specimen Banks (NNHBSB)

The Brain Mapping Foundation (BMF) calls for the creation of a National Network for Human Brain and Specimen Banks (NNHBSB), which would work closely with existing organ, harvest teams and specimens banks across the country. This program could be implemented by the Department of the Health and Human Services (HHS). This database would include A) Postmortem data and B) Brain imaging data from living humans including patients with neurological disorders.

A. Postmortem Data: The NNHBSB could coordinate the harvest of donated brains from all organ donors and connect the specimens (including Brain, Cerebrospinal Fluid, eyes, spinal cord) with data from the electronic medical record of the patient to maximize what we are able to learn from the brains about conditions such as degenerative brain disease and traumatic brain injury. The bank would include both brains with known disease as well as ostensibly healthy brains. This national network would have far greater power to enhance our knowledge than existing institutional or regional programs.

B. Brain Imaging and Activity Maps: Brain imaging techniques have revolutionized the way we can study the human brain but in order to harness the potential to improve human health it is crucial to study both animals and living humans, both healthy and those with a variety of brain illnesses at the organ, tissue, cellular and subcellular levels (Levy 2013). Data from multiple modalities such as functional and structural MRI, DTI (HTDI, HFDTI, etc.), CT, Ultra-low field MRI, PET, noninvasive and surgically implanted brain and spinal cord stimulation devices can be compared and related to preclinical models of disease to provide the most powerful approach to understanding and advancing human brain health. Clinical applications of functional brain maps will require large populations to ensure the results sample a broad spectrum of the population cohort, both in health and disease. Longitudinal studies will be required, to examine aging, consequences of interventions and to establish stability of results. This in turn will require integration and standardization of methodology across multiple centers around the US, in order to perform the measurements in a useful time frame. This means attention must be focused on expanding multicenter brain mapping methodology such as has been developed by the Alzheimer's disease Neuroimaging Initiative and the FIRST Biomedical Imaging Research Network. Generating a broad series of brain maps is a truly multidisciplinary effort that will involve many scientists and clinicians. Next-generation brain mapping would highly benefit from integrating novel concepts such as cytomics, also referred to as spatial systems biology that is revolutionizing our knowledge about cellular interactions and signal transduction towards therapeutic intervention: by combining imaging-derived and genomic data in a cell-by-cell mode (Pierzchalski et al. 2008; Kriete 2005; Valet et al. 2003; Gertych et al. 2009; Tajbakhsh et al. 2011). Cytomics would apply bioinformatics to understand the relation between molecular composition, topology and functionality of cells in neural circuits. Translation of brain maps to studying and curing disease will require careful coordination of technology providers, basic scientists and clinicians with diverse viewpoints. The successful conclusion of this program will provide normative data that will be invaluable in studying the special needs of diverse patient groups. Therefore, helping with the development of customized and personalized medicine. To summarize: the program must be multimodal, multi-institutional, must include preclinical studies, and sample a broad demographic profile.

National Data Repository and Analysis for Neuroscience (NDRAN)

The Congressional Accountability Office documents that $2.7B in research funding has been provided to the DoD to address Traumatic Brain Injury (TBI) and Psychological health over the past 5 years, while NIH has spent another $405M. However, despite 3.1B+ in federal spending in the last 5 years on TBI and psychological health, we have not had a significant return on our investment. Progress in treating these disorders has been slow, and new therapies have yet to emerge.

In order to avoid duplication of effort, more closely monitor progress, identify particularly promising work and ensure efficient use of funds, we need to establish an electronic system that encompasses all areas of neuroscience and clearly documents the results. Funded research needs to be outcome-driven with attention to deliverables, timelines and cost-effectiveness. The NDRAN could help to achieve these aims. We believe that 3 different levels of access to the repository could be established.

1. Patient Education: One level for patients could educate them about the latest research linking to articles in Pubmed Health (http://www.ncbi.nlm.nih.gov/pubmedhealth/) and opportunities to participate in research (http://www.clinicaltrials.gov/).
2. Large Scale Research Collaboration: A second level would facilitate, incentivize, and target barriers to collaboration among researchers. For example, patient data donated to the

repository and development of tools to facilitate data quality and comparability across sites would be considered as accomplishments in evaluating research productivity. Bringing together data from diverse sources and studies will allow clinicians to base decisions on large, definitive, studies rather than small, inconsistent, studies.

3. Government Oversight of Public Health Needs, Service Delivery Efficiency, and Barriers to Moving Innovations to Clinical Care: The final level would allow multiple government agencies to access the data and systematically analyse, and produce publications to identify research gaps, barriers to rapid and efficient implementation of best clinical practices, and guide future funding. This level would also identify and consider burdensome regulatory barriers and delays that do not protect patient safety and which limit patient access to effective therapies and sensitive diagnostic tools.

One clear need is to have people working in different silos of neuroscience (usually characterized by working on problems in different "points" within the time and spatial parameter scales) be able to communicate and exchange information with each other, rather than remain in their scientific cliques, sometimes for their entire careers. To accomplish this neuroscience data repository and analysis it would be useful to bring diverse interest groups together under one umbrella; NDRAN is designed to accomplish this goal. NDRAN also could identify important life saving technologies such as High Definition Diffusion Tensor imaging, biophotonics, nano platforms, non-invasive multimodality imaging technologies (UV, IR, Ultra Low MRI, etc.) technologies and devices in order to introduce a new generation of life saving technologies, help reduce the cost of health care, and increase efficiency in delivering personalized medicine, which will be "outcome driven."

PURPOSE

As described previously, the SBMT and BMF proposed to the White House, NIH and DARPA (Defense Advance Research Program Agancy) 3 national strategic programs:

- National Alliance for NanoBioElectronics (NANBE)
- National Network for Human Brain and Specimen Banks (NNHBSB)
- National Data Repository and Analysis for Neuroscience (NDRAN)

The program would be established in order to:

1) Foster partnership in technology, science, and medicine through the development of national consortia.
2) Systemically and actively facilitate the integration, translation and commercialization of technologies and scientific advancement from various physical, social, and biological sciences into clinical medicine.
3) Establish consortia, scholarships and educational programs at all educational levels in order to encourage ingenuity and cross-disciplinary interaction, which could contribute to the development of future scientists, technologists and health professionals.
4) Promote education curricula addressing disease prevention. This novel program will contribute to US leadership in the global healthcare market place while building long term employment.
5) Establish brain mapping centers, minimally invasive and noninvasive technologies such as nanotechnology, biophotonics, ultra low MRI, portable CT, High definition Diffusion (HDTI) Tensor Imaging, simulations, cellular therapeutics/stem cell and devices, and these methods could help to map the brain and help physicians treat neurological disorders as well.

SIGNIFICANCE OF THE PROPOSED APPROACH AND ITS IMPACT ON THE FIELD OF BRAIN MAPPING

This 3-tiered proposal including NANBE, NNHBSB and NDRAN, is designed to achieve the following goals:

(1) Create jobs in the biotech sector through investment in research. This program will both directly and indirectly support technology, science, healthcare, medical research and related fields.
(2) Improve healthcare efficiency and cost-effectiveness through the identification of best practices and the promotion of personalized medicine, point of care diagnostics, electronic medical records and advance information technology such as grid technology. Grid technology allows hospitals to be connected to each other. This will reduce healthcare cost, increase efficiency and prevent medical errors.
(3) Stimulate small businesses through expanded SBIR and SBA programs.
(4) Promote disease prevention to reduce healthcare costs.
(5) Assemble multisite consortiums to advance the study of neurological diseases, including brain mapping, traumatic brain and spinal cord injuries, PTSD, neuro-oncology and neurodegenerative diseases. The programs will scientifically evaluate and apply the latest technologies in neuropharmacology, nanobioelectronics, nanoneurosurgery, nanoneuroscience, imageguided therapy, frontiers in stem cell research, therapeutics and regenerative medicine (Sidhu 2012), device, and nanotechnology.
(6) Translate medical research and discoveries to the social sciences including behavioral studies and neuro-economics.
(7) Foster education in neuroscience and related disciplines by supporting programs and scholarships at the K-12 such as SBMT kids corner, the high school, university such as SBMT student chapters, and postgraduate levels such as our fellowship programs to encourage cross-disciplinary thinking and interest in related fields.
(8) Advanced training for workers and professionals in the US.
(9) Promote US leadership in technology, healthcare policy, medical research, and science.
(10) Complement the missions of all participating agencies and allow them to be more productive by facilitating cross disciplinary activities and reducing wasteful spending, duplication and medical errors.

PROGRAMS AND METHODS

In order to assess the viability, novelty, and success of the proposed program, SBMT and BMF have contacted officials from many US government agencies. A multidisciplinary approach involving scientists, engineers, physicians, surgeons, legal scholars and economists is necessary to achieve the ultimate goals of the program. To implement this program SBMT and BMF propose to the White House Office of Science, Technology and Policy (OSTP) to assemble leading experts from, foundations, academia and industry. White House OSTP, NIH, NSF and DARPA along with other government and other nonprofit and industry partners will play a central role in coordinating these programs. Leading foundations and associations should be part of these unique consortia. These programs will be responsible for defining the programmatic goals, organizing the consortia, requesting proposals, distributing funds, and reporting back to the Congress and the executive branch through quarterly reports. This should foster rapid growth in healthcare-related jobs, the creation of a sustainable infrastructure, and continued US leadership in the healthcare sector.

Representatives from involved public and private partners and agencies will participate in an Oversight Committee to make sure that funds are spent properly and with transparency. The NANBE in Collaboration with National Institute of Health will request proposals for the development of the

consortia. The proposals must include multiple centers and institutions within the US and explain in detail how funds will contribute to job creation in multiple fields using science, engineering, education and technology transfer. While this initiative is designed for national consortia, international participants whose country(ies) match the funds, effort and protect the intellectual property of US investigators are welcome to join this effort if and when they agree to invest at least up to 20% of their funds in the US. Participation from industry and private foundations is also welcomed provided that they too bring commensurate funds or efforts, and show how their participation will foster job creation using neurosciences.

This proposal will also promote scholarships, fellowships, and humanitarian work by physicians and scientists working in collaboration with other humanitarian organizations, government agencies and foundations. In conjunction with its government partners, this SBMT and BMF-proposed program will create the world's largest multidisciplinary research consortium for treatment of neurological diseases, with a focus on job creation and technology development by providing incentive/bridge grants for spinoffs and biotech formations.

CONCLUSION

It is our strong belief that no single foundation or organization should spearhead President Obama's Brain Mapping Initiative. Prominent organizations like ours have been on the forefront of brain mapping and therapeutics for decades. Therefore, the national policy must be shaped through an inclusive process, which is transparent and open to the public. Scientists at the grassroots level should be able to voice their opinion so that new ideas can be cultivated. Moreover, there is a great need for training a new generation of cross disciplinary scientists. In this regard, Brain Mapping Foundation is partnering with one of the prominent universities in the US to establish a doctoral program in NanoBioElectronics, which will train a new generation of scientists who could integrate nanotechnology, device, imaging and cellular/stem cell therapy. We also believe that standardization of the brain mapping field and technologies are the key to the advancement of the field. In this regard SBMT is launching the American Board of Brain Mapping, which will focus on certifying specialists (PhDs and MDs) in the field, in partnership with industry and pertinent governmental agencies.

The programs described in this chapter, which were also submitted to the White House in a "White Paper", are aimed at building national and global consortia, which could bring increased investments to domestic and international partners, and help to dramatically change the field of neuroscience by distinguishing between projects/areas that need resources and those that are less meritorious. These proposals address the "valley of death" by establishing a path extending from integration to translation and into commercialization. This could improve the efficiency and cost-effectiveness of research while enhancing the evaluation of neurological disorders and creating biotech jobs in the US. We strongly believe that funded research has to be outcome-based. Research policies should focus on how to avoid duplication, how to encourage camaraderie in research, and how to properly reward partnership and collaborations. This proposal could enable scientists to have open access to the work done by other scientists in real time, and help build consortia, which are not aimed at "competing amongst institutions but competing against the diseases," said Babak Kateb, Founding chairman of the Board of SBMT, President of Brain Mapping Foundation and Research Scientist at the Department of Neurosurgery at Cedars Sinai Medical Center, CA, USA.

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