DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY COUNCIL FOR BIOMEDICAL IMAGING AND BIOENGINEERING

Summary of Meeting[1]
January 23, 2015

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 37th meeting on January 23, 2015, at the Bolger Center in Potomac, Maryland. Dr. William Heetderks, Associate Director of Science Programs of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), presided as Council chairperson. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. to 1:00 p.m. for review and discussion of program development, needs, and policy. The meeting was closed to the public from 2:00 p.m. to 2:15 p.m. for the consideration of grant applications.

Council members present:
Dr. Kristi Anseth, University of Colorado, Boulder, Boulder, CO
Dr. Carol Espy-Wilson, University of Maryland, College Park, MD
Dr. John C. Gore, Vanderbilt University Medical Center, Nashville, TN
Dr. Cato T. Laurencin, University of Connecticut, Farmington, CT
Dr. Raphael Lee, University of Chicago, Chicago, IL
Dr. Mark Musen, Stanford University, Stanford, CA
Dr. A. Gregory Sorensen, Siemens Healthcare North America, Malvern, PA
Dr. Daniel Sullivan, Duke University Medical Center, Durham, NC
Dr. James Thrall, Massachusetts General Hospital, Harvard Medical School, Boston, MA
Dr. Bruce Tromberg, University of California, Irvine, CA
Dr. Sheldon Weinbaum, The City College of New York, New York, NY

Ex officio members present:
Dr. P. Hunter Peckham, U.S. Department of Veterans Affairs, Cleveland, OH
Dr. Sohi Rastegar, National Science Foundation, Arlington, VA
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences, Bethesda, MD

Council Members absent:
Dr. Karen Hirschi, Yale University, New Haven, CT

Ex officio members absent:
Ms. Sylvia M. Burwell, U.S. Department of Health and Human Services, Washington, DC
Dr. Francis Collins, National Institutes of Health, Bethesda, MD
Dr. Anne Plant, National Institute of Standards and Technology, Gaithersburg, MD

Chairperson:
Dr. Roderic I. Pettigrew (Via telephone due to illness)

Executive Secretary:
Dr. William Heetderks

[1] For the record, it is noted that members absent themselves from the meeting when the Council is discussing applications (a) from their respective institutions or (b) in which a conflict of interest may occur. This procedure only applies to applications that are discussed individually, not to "en bloc" actions.

Also present:

NIBIB staff present for portions of the meeting:

Dr. Maria Aranova
Ms. Holly Atherton
Mr. Angelos Bacas
Dr. Richard A. Baird
Ms. Barbara Cantilena
Ms. Shirley Coney-Johnson
Dr. Richard Conroy
Ms. Christine Cooper
Ms. Zoe Ann Copeland
Ms. Monique Day
Dr. Anthony Demsey
Dr. Emilios Dimitriados
Mr. Jeff Domanski
Dr. Henry Eden
Ms. Kate Egan
Ms. Angela Eldridge
Ms. Kathryn Ellis
Dr. Zeynep Erim
Mr. Anthony Fransella
Dr. David George
Ms. Pam Glikman
Dr. Ruth Grossman
Dr. John Hayes
Ms. Eunica Haynes
Ms. Alisha Hopkins
Mr. Jake Hoyne
Mr. James Huff
Dr. Rosemarie Hunziker
Mr. Tom Izzard
Dr. Tom Johnson
Dr. Chris Kelley
Ms. Margot Kern
Dr. Steven Krosnick
Dr. Tiffani Bailey Lash
Dr. Richard Leapman
Dr. Christina Liu
Dr. Guoying Liu
Dr. Xiao-Zhong (James) Luo
Dr. Shadi Mamaghani
Dr. Rishi Mathura
Ms. Jessica Meade
Mr. Todd Merchak
Mr. Joe Mosimann
Dr. Peter Moy
Dr. Gang Niu
Dr. Vinay Pai
Dr. Grace Peng
Mr. Mohammed Rahamatullah
Ms. Vicki Rein
Dr. Mary Rodgers
Dr. Antonio Sastre
Mr. Shaun Sims
Mr. Russell Songco
Dr. Jessica Tucker
Ms. Florence Turska
Mr. Kwesi Wright
Ms. Li-Yin Xi
Dr. Ruixia Zhou
Dr. Steven Zullo

Non-NIBIB National Institutes of Health (NIH) employees:

Dr. L. Michelle Bennett, NHLBI
Dr. Simhan Danthi, NHLBI
Dr. Jill Heemskerk, NIMH
Dr. Michael Lauer, NHLBI
Dr. Ed Ramos, OD

Members of the public present for portions of the meeting:

Ms. Erin Cadwalader, Lewis-Burke Associates, Washington, DC
Mr. Frank Guest, National Capitol Captioning, LLC
Dr. Mercedeh Khajavikhan, University of Central Florida, Orlando, FL
Dr. Jeff Lichtman, Harvard University, Cambridge, MA
Mr. Michael Peters, American College of Radiology
Mr. Will Portobanco, Bolger Center
Mr. Nick Rooney, National Capitol Captioning, LLC
Dr. Bruce Rosen, Massachusetts General Hospital, Charlestown, MA
Ms. Kathy Sedgwick, NOVA Research Company

I. Call to Order: Dr. William Heetderks

Dr. William Heetderks called to order the 37th meeting of the National Advisory Council for Biomedical Imaging and Bioengineering. He reminded attendees that the morning session of the meeting was open to the public, and welcomed attendees. He noted that Dr. Pettigrew was unable to attend due to illness but was listening via telephone.

II. Director's Remarks: Presentation given by Dr. William Heetderks

A. Remembering Dr. Ferenc A. Jolesz

Dr. Heetderks acknowledged the work of Dr. Ferenc A. Jolesz, a major contributor to the imaging field, who died December 31, 2014.

B. NIBIB Awards and Honors

Several members of the NIBIB "family" have received distinguished honors and awards. Three were inducted into the National Academy of Engineering: former NIBIB Council Member Dr. Katherine Ferrara; NIBIB grantee Dr. Charles Mistretta; and Dr. Harrison Barrett, the first NIBIB MERIT Awardee.

The 2014 Nobel Prize in Chemistry was awarded to Drs. Eric Betzig, Stefan Hell, and William E. Moerner for the development of super-resolved fluorescence microscopy. Dr. Moerner was a member of the NIBIB Board of Scientific Counselors. Dr. Betzig worked closely with two NIBIB intramural investigators, Drs. George Patterson and Hari Shroff.

The Academy of Radiology Research presented Dr. Pettigrew with the inaugural Academy Gold Medal at the annual Radiological Society of North America meeting in December, which also featured an address from NIH Director Francis Collins.

C. New Council Member, Council Liaison, and NIBIB Staff

Dr. Heetderks welcomed Dr. Carol Espy-Wilson as a new member of the Council. Dr. Espy-Wilson is a professor of electrical and computer engineering at the University of Maryland, and CEO and founder of Omni Speech, a company that designs software for enhancement of electronic voice communications.

Dr. Heetderks introduced Dr. Bruce Rosen, who is the Council's liaison to the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Multi-Council Working Group. Dr. Rosen is an expert on functional neuroimaging and a professor of radiology at Harvard Medical School.

Dr. Jill Heemskerk joins NIBIB as Director of the Office of Research Administration in February. Dr. Heemskerk's background is in developmental neurobiology and genetics; she comes to NIBIB after 15 years at NIH overseeing preclinical and clinical translational research.

D. NIH Fiscal Year 2015 Budget and Legislation

The Fiscal Year (FY) 2015 NIH budget is $30.3 Billion, an increase of 0.8 percent over FY14. NIBIB's FY15 budget is $327.2M, which represents a 0.1 percent increase over FY14. The current payline is the 9th percentile, with the Expanded Opportunity Zone (EOZ) for select funding between the 9^{th} and 18^{th} percentiles.

Since 2009, NIBIB has seen a significant increase in the number of highly-scored grant applications. The number of applications scoring at the 10^{th} percentile rose from 73 in FY09 to 123 in FY14.With a relatively flat budget over this period, the large increase in highly-scored applications has substantially reduced the percentile payline.

The FY15 NIH budget includes specific increases for Alzheimer's disease, BRAIN, implementation of the Gabriella Miller Kids First Research Act, and Ebola. In addition, there is language in the NIH budget report addressing concerns about funding early-stage investigators; the average age at which an investigator first obtains R01 funding is 42, and there is a desire at NIH to lower that average age.

The Commerce, Justice, Science Appropriations Bill is calling for the White House Office of Science and Technology Policy, in cooperation with NIH, to establish a committee on medical imaging to coordinate federal imaging research investments.

E. NIH ACTIVITIES

Presidential Visit to NIH

President Obama visited the NIH campus on December 2, 2014, touring the NIH Vaccine Research Center, where he viewed a demonstration on how to make a vaccine.

Common Fund Activities

NIBIB is co-leading two NIH Common Fund initiatives: Stimulating Peripheral Activity to Relieve Conditions (SPARC) and Single Cell Analysis. The SPARC program is built on the notion that modulating the signals of the peripheral nervous system that control organ function is a potentially powerful way to treat many diseases and medical conditions. The goal of SPARC is to understand the function of the peripheral nervous system and thus catalyze development of neuromodulation therapies. SPARC projects are funded with a $248 million investment over 6.5 years. About half of these funds will be used to support functional mapping of the circuits; $65.5 million has been set aside for development of next-generation tools, $31.5 million for off-label use of market-approved technology, and $12.5 million for data coordination. Dr. Pettigrew co-chairs the NIH committee and NIBIB's Drs. Grace Peng and Vinay Pai are taking the lead on particular initiatives.

The Single Cell Analysis initiative has issued a "Follow That Cell" Challenge with a goal of developing novel analytic methods to detect and assess changes in individual cell behavior and function over time. In the first phase, competitors provided a theoretical description of the proposed method; prizes will be announced March 16, 2015. In the second phase (2015–2017), competitors must reduce those ideas to practice. Dr. Richard Conroy, director of NIBIB's Division of Applied Science & Technology, co-leads this NIH Common Fund activity.

NIH BRAIN Research Priorities

During FY14, 58 awards were made to support NIH BRAIN research priorities: cell-type classification, novel tools for mapping circuits at multiple scales, next-generation human imaging, large-scale recording and modulation of neural activity, and integrating new technological and conceptual approaches to discover how dynamic patterns of neural activity are transformed into cognition, emotion, perception, and action in health and disease. With an emphasis on novel tool development and human imaging, this initiative is of high interest to NIBIB. Funding announcements and initiative updates are available at http://braininitiative.nih.gov.

F. NIBIB ACTIVITIES

Reverse Paralysis Consortium

Supported by the Reeves Foundation, the Reverse Paralysis Consortium convenes stakeholders in addressing paralysis with a goal of expanding testing of the spinal stimulation approach, shown by NIBIB grantees Drs. Reggie Edgerton, Susan Harkema and colleagues to have promise for improving quality of life and restoring voluntary movement in individuals who had been paralyzed due to spinal cord injury.

The November 2014 consortium workshop was attended by 40 researchers and representatives from reverse paralysis organizations, the U.S. Food and Drug Administration (FDA), medical device companies and the NIH. The consortium meets again in February 2015.

NIBIB-NCI Collaborations

NIBIB and the National Cancer Institute (NCI) are natural partners for research collaborations. Active collaborations to date include a conference on Point of Care (POC) Technologies for Cancer and funding announcements in POC technologies, multiscale modeling, and drug delivery. NIBIB and NCI program staff will meet on February 6 to identify additional scientific opportunities that the two Institutes can address jointly, and discuss areas for effective leveraging of funds.

Bill and Melinda Gates Foundation

NIBIB has been working with the Bill and Melinda Gates Foundation (BMGF) in supporting development of POC technologies for use in low-resource settings. Joint NIBIB/BMGF leadership will be involved in the Institute of Electrical and Electronics Engineers (IEEE)/Engineering in Medicine & Biology Society (EMBS) Healthcare Innovations and Point-of-Care Technologies Conference that NIBIB is hosting in November 2015. NIBIB and BMGF have identified a focus on the eradication of malaria as a possible collaborative effort.

Quantum Program

The funding opportunity announcement for the NIBIB Quantum Program has been re-issued. This highly successful program focuses on quantum technological advances for major diseases and public health programs. The next receipt deadline for these awards is January 26, 2015.

G. Science Highlights

Cancer Vaccine Development

Drs. David Mooney, Glenn Dranoff and colleagues are testing an injectable self-associating polymer cancer vaccine as an alternative to current immunotherapies. This biomaterial-based vaccine uses a silica rod solution to deliver the vaccine; after injection, the silica rods self-assemble to recruit and activate dendritic immune cells to fight the tumor. This approach has shown promising results in mouse models, decreasing tumor volume and increasing survival.

Focused Ultrasound in Development for Alzheimer's Disease

Focused ultrasound is being studied for its ability to open the blood-brain barrier, which has a number of potential clinical applications. Dr. Kullervo Hynynen and his research team showed that focused ultrasound treatments improved pathologic abnormalities and behavior in a mouse model of Alzheimer's Disease. The treatment succeeded in reducing the size and number of the plaques that are a hallmark of Alzheimer's Disease.

Compressed Ultrafast Photography

Dr. Lihong Wang and his team at Washington University have developed an ultrafast camera that captures images at 100 billion frames per second. This imaging method allows, for the first time, visualization of events such as the movement of light pulses. The ability to watch ultrafast events in motion is expected to yield novel discoveries in a wide range of fields, including biomedical research.

III. Task Force Report: Dr. Bruce Tromberg

Dr. Bruce Tromberg outlined discussions of the NACBIB Task Force on Strategies for Efficient Use of Research Dollars. Formed after the May 2014 Council meeting, the task force is charged with reviewing needs, opportunities, and available resources to advance the NIBIB mission, and with developing recommendations for how best to use limited resources. The primary issue is that, at the 9th percentile, the NIBIB payline is too low for NIBIB to fund many promising, potentially impactful ideas, technologies, and people. As a consequence, the NIBIB community has become increasingly concerned about the viability of technology based research programs and important subfields have become marginalized as they compete with "hot" new fields for limited resources.

The task force has established several goals, beginning with moving the payline into double digits. The target is the 12th percentile in the current fiscal year, followed by one percentile increases per year to reach the 15th percentile. Additional goals for optimizing and enhancing NIBIB impact include the following: increasing the number of investigators and diversity of NIBIB awards; developing new concepts to support investigators at critical points in their careers; assessing whether the current structure has created funding inequities for underrepresented minorities, women, young investigators, and new applicants; and improving community morale by fostering a spirit of inclusiveness and desire to contribute to the NIBIB mission. Finally, the task force aims to promote NIH by highlighting NIBIB's role in fostering a culture that helps drive economic growth—through the creation of intellectual property, jobs, and commercialization of new methods and technologies.

The task force recommends a number of practical actions that may enable NIBIB to accomplish these ambitious goals.

The cost of increasing the payline is about $3 million per year per percentile point. The task force proposes directing additional funding to the payline by: (1) freeing up resources through reallocation, redistribution, and restructuring of the current resources, and (2) leveraging available funds via the formation of strategic partnerships. Task force recommendations include: In the submission phase, encourage limited budgets and focused aims (e.g., small R01s) that demonstrate cost-effectiveness. In the pre-award phase, give NIBIB programs enhanced flexibility to identify promising out-of-payline applications and negotiate funding those at a reduced cost. In the award phase, increase Type 1 and Type 2 administrative budget reductions to align with those of other NIH Institutes.

The task force proposes creating a full-time position for developing strategic partnerships and reviewing and marketing the NIBIB portfolio to determine optimal areas for synergy and potential partners such as nonprofits, government agencies, and other NIH Institutes.

The task force offers several new concepts for supporting investigators: creating new award mechanisms for individuals at different career stages; using award mechanisms that require service to the NIBIB community, e.g., via participation in review panels; putting constraints on the number and type of awards held concurrently; restricting the number of consecutive K awards without R award funding; and creating prestigious individual investigator awards with special career development opportunities built in.

Task force discussions were informed by key investigator metrics that NIBIB staff provided. Between 2008 and 2014, the number of R01 applications has been stable (ranging between 418 and 433); however, the number of R21 applications has increased consistently over time (i.e., from 339 to 699). New applicants submit about 40 percent of applications, with 70 percent scoring in the top 10th percentile. This suggests that NIBIB favors support of new principal investigators (PIs).

In an effort to build and foster the NIBIB community, the task force recommends forming review panels with membership that will preserve the concepts and intent of proposed new mechanisms. For example,

one goal might be to stimulate true high-risk R21 awards. This could be accomplished by forming panels of new NIBIB investigators who are receiving K and R35 awards.

The outlook will improve with rising paylines, enhanced service to NIBIB from K and R35 recipients, and transparent sharing of NIBIB's mission to address these challenges. Hopefully, the NIBIB community will recognize the importance of shared sacrifice in difficult times and respond in a positive way.

Discussion

Dr. Weinbaum suggested screening the R01s, many of which include multiple investigators, to see how support for senior investigators compares with junior investigators. He also suggested that sending the message that new applicants do well at NIBIB will encourage the many underfunded women and minorities to stay in research.

Dr. Rosen commented that the success of new investigators at NIBIB is good news, but the converse is that "not new" applicants are not succeeding. He asked whether the reasons for this trend are known. Dr. Heetderks responded that the answer to this question is still under investigation. Dr. Weinbaum suggested that young investigators may be submitting more exciting, more novel ideas than senior investigators who are seeking support for important, but ongoing, work.

Dr. Tromberg indicated that creating alternative mechanisms should draw applicants and perhaps reduce existing and emerging disparities.

Dr. Laurencin asked whether EOZ approaches other Institutes are using have an impact on underrepresented minorities. Should the EOZ be used to increase diversity of the applicant pool? He also opined that if consistently successful investigators knew that long-term funding would be available they would be comfortable getting smaller grants.

Dr. Tromberg stated that the task force will request a deeper look into data on where underrepresented minorities stand at NIBIB. Regarding selection of applications in the EOZ, he asked that Council members continue to engage in the decision-making process.

Dr. Lee commented that there must be data on the practice of adjusting funding levels that the task force is recommending, and on whether there is a return on investment for making these changes. This will be important for predicting the impact of the proposed changes. Dr. Tromberg responded that the problem can be distilled down to an unacceptably low payline. Success of the changes will be assessed based on whether NIBIB succeeds in increasing the payline and increasing diversity of investigators and types of activities supported. Once the Institute has recovered this ground, other outcomes can be explored.

Dr. Sorensen remarked that the problem with the payline is that the denominator—the number of applications submitted—has increased, and universities are not carrying their fair share. The R01 application rate is stable, whereas the R21s have doubled. That suggests that something else is at work here. Dr. Tromberg noted that this phenomenon is NIH-wide and suggested that the R21 has moved away from its original intent of supporting innovative ideas. The task force proposes creating a mechanism that offers special opportunity funds for investigators, drawing them away from applying for R21s.

Dr. Gore commented that established investigators will find it hard to change their strategy for obtaining funding. Dr. Tromberg added that the increasing administrative burden on senior investigators diminishes their ability to put time and effort into innovative thinking.

SBIR Informatics Program Announcement

Dr. Heetderks explained that the task force had been asked to consider a proposed informatics program announcement using the R44 SBIR mechanism. Eleven NIH Institutes would participate, including NIBIB.

Council approved the concept of the proposed announcement.

IV. BRAIN Initiative Working Group Report: Dr. Bruce Rosen

Dr. Rosen presented an overview of the BRAIN initiative and activities of the BRAIN Multi-Council Working Group on which he serves as NIBIB Council liaison.

In April 2013, President Obama introduced the BRAIN initiative, which focuses developing innovative neurotechnology tools scientists need to get a dynamic picture of the brain in action, and this goal meshes exceedingly well with the NIBIB mission. Organizing principles for the initiative were set out in the June 2014 report entitled "BRAIN 2025: A Scientific Vision".

Noting that the first round of grants has been funded, Dr. Rosen presented snapshots of projects that represent the initiative's research priorities. Projects include a census of cell types, tools for cells and circuits, new technologies for large-scale recording and modulation, understanding of neural circuits, and next-generation human imaging.

BRAIN awardees attended a two-day workshop that included breakout sessions organized by key areas to allow investigators to discuss possible collaborations. Dr. Rosen noted that many good ideas arose during breakout sessions.

A number of Requests for Applications (RFAs) have been reissued. Notices of intent have been published to announce solicitations of new concepts and early-stage research for: (1) large-scale recording and modulation in the nervous system; (2) clinical studies to advance next-generation invasive devices for recording and modulation in the human central nervous system; and (3) research opportunities using invasive neural recording and stimulating technologies in the human brain.

Discussion

Dr. Sorensen commented on the importance of keeping the work focused on what has potential for practical human application. Researchers need to keep in touch with the fact that the funding community is interested in how people will quickly benefit from their work.

Dr. Gore said that he understands that proposed work to advance existing technology such as functional magnetic resonance imaging (fMRI) has been viewed as nonresponsive to the BRAIN RFAs, yet fMRI is state of the art for looking at systems in humans. Dr. Rosen indicated that Dr. Gore's perception is correct and that part of his own mandate as NIBIB liaison is to advocate for inclusion of advances in existing technology.

V. Review of Council Procedures and Regulations: Dr. William Heetderks

Dr. Heetderks welcomed visitors and members of the science press and scientific society constituencies. He noted for the record that a quorum was present for this Council meeting. Dr. Heetderks acknowledged Dr. Anthony Demsey for his contributions in preparation for conducting this Council meeting, and thanked Ms. Pam Glikman and Ms. Alisha Hopkins for coordinating meeting logistics.

A. Council Regulations, Policies, and Procedures

Dr. Heetderks reviewed conflict-of-interest, confidentiality, and lobbying guidelines.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is set for Friday, May 15, 2015 (subsequently, the date was moved to May 18 due to unavailability of meeting space). Dr. Heetderks asked Council members to inform him about conflicts with any of the upcoming meeting dates listed at the bottom of the agenda.

C. Approval of the September 16, 2014, NACBIB Meeting Minutes

A motion to approve minutes of the September 16, 2014, NACBIB meeting was forwarded, seconded, and approved unanimously.

D. Reaffirming Council Operating Procedures

Dr. Heetderks referred to the Council Operating Procedures that had been distributed to the Council electronically prior to the meeting. The document contains one minor change to clarify rules around special council review of applications from investigators whose research grant support exceeds $1M. A motion to reaffirm the Council Operating Procedures was forwarded, seconded, and approved unanimously.

E. Biennial Report on Monitoring Adherence to Policies Governing Gender and Minority Inclusion

Dr. Heetderks noted that the report on monitoring adherence to policies governing gender and minority inclusion had been included in the electronic Council book. On behalf of the Council, the report will be forwarded to the NIH Tracking and Inclusion Committee.

VI. Perspectives from NHLBI on Portfolio Prediction and Performance: Dr. Michael Lauer

Dr. Lauer described his analysis of research funded by the National Heart, Lung, and Blood Institute (NHLBI), where he is Director of the Cardiovascular Division (CVD). He highlighted a *Science* editorial in which the author said that the U.S. system for funding research is failing because it is based on an assumption of continuous growth. The reality is that research funding is contracting, which puts pressure on funding agencies to predict with accuracy which projects will have the most impact and thus are worthy of funding.

To predict project success, funding agencies primarily use peer review. The Cochrane Collaboration's systematic review on the use of peer review concluded that there is scant evidence to support this practice. Others have described peer review as "imprecise" and "prone to bias." Still others claim that, due to flaws in the peer review system, as many as one-third of current grants are awarded essentially at random.

Measuring the impact of research is difficult. Dr. Lauer described a Rand Corporation study commissioned by the American Association of Medical Colleges, which grouped measures of research impact into two categories: (1) high-intensity evaluation of small samples (e.g., peer review, site visits, document review, and interviews); and (2) high-volume evaluations (e.g., bibliometrics, economic analysis, and data mining). Drs. Muin Khoury (NCI) and John Ioannidis (Stanford University School of Medicine) described another approach for measuring impact: the Productivity, Quality, Reproducibility, Sharing, and Translation (PQRST) Approach.

Dr. Lauer and his colleagues measured productivity of 1,492 R01 grants funded by the NHLBI CVD between 2001 and 2008 by counting the number of highly cited publications arising from each study. A highly cited publication is defined as being in the top 10 percent of citations in that scientific field for a particular year of publication. Results of their analysis showed, for applications scoring in the funded range, there was no association between the grant's original percentile ranking and productivity. In further analysis of these data, Dr. Lauer assigned PIs to two groups—high and low—based on their

publication productivity during the five years prior to their grant submission. Findings indicate that subsequent research led by PIs with a record of high productivity yielded higher citation impact than those with a history of lower productivity. The findings support the notion that future achievement can be predicted with fair accuracy based on previous achievements.

Dr. Lauer noted study limitations including the use of a single metric (citation impact) and review of grants within a single division at NHLBI awarded during a limited time span. He also described the difficulty of measuring how much an NHLBI grant contributed to publications that list multiple funding sources.

Dr. Lauer collaborated with staff at the National Institute of Mental Health (NIMH) to see if the results would be the same. They applied the same methodology to look at 1,800 NIMH grants awarded over a ten-year period. Consistent with the findings on NHLBI grants, results of this analysis showed no association between a grant's original percentile ranking and productivity. Dr. Lauer and his colleagues also looked at predicting productivity of clinical trials on the basis of how rapidly results are published. It has been suggested that the primary results of a number of completed NIH clinical trials were published after a substantial delay or not published at all. A survey of 244 cardiovascular trials funded over an 11-year period showed that fewer than 60 percent were published within 2.5 years of completion. Results of a review of NHLBI clinical trials grants showed no correlation between peer review scores and how rapidly trial results were published.

Additional analysis revealed two good predictors of time to publication: clinical endpoints (e.g., premature death, stroke, or heart attack) and higher investments (up to about $5 million). Trials that focus on clinical endpoints were published quickly, whereas those that focused on surrogate endpoints were published much more slowly, with only 10 percent publishing results within one year of completion.

It has been suggested that journals are averse to publishing negative trials. Dr. Lauer found that positive trials did publish more than negative trials, but only by a small degree.

NIH Institutes are considering a variety of alternative models. For example, NIGMS is looking at the investigator-based R35 mechanism, which allows the Institute to consider prior achievements as a predictor of future success. NIBIB's Expanded Opportunity Zone (EOZ) to consider select funding of applications outside the automatic payline is another data-driven alternative approach.

Dr. Lauer concluded by noting that no system is 100 percent successful. Rather, the funding institution's goal should be to increase the "hit rate" and reduce "false positives" in funding decisions.

Discussion

Dr. Sorensen asked what changes NHLBI has implemented following Dr. Lauer's analysis. Dr. Lauer responded that the Institute is revamping the way it conducts clinical trials. A larger proportion of the NHLBI portfolio is focused on hard clinical rather than surrogate endpoints, and they are using an EOZ approach to fund applications outside the payline.

Dr. Rosen asked what evidence NHLBI has that projects selected in an EOZ will be better than those selected based on review scores alone. Dr. Lauer answered that NHLBI is following projects prospectively, which will require a long follow-up period. He added that the National Institute of Arthritis and Musculoskeletal and Skin Diseases and other NIH Institutes that employ similar "select pay" approaches have reported increased productivity.

Dr. Weinbaum commented that selection criteria are not properly weighted: past performance counts for only 20 percent of how a proposal is rated. At the same time, it is unfair to compare PIs of different ages and widely varying years in the field.

Dr. Tromberg noted that he was very impressed with peer review in the 1990s. Since then, the system has gone through a perfect storm—the combination of the budget crash and multiple changes in the guidelines. He asked Dr. Lauer if he uncovered any evidence during his studies that peer review might have been more effective in the 1990s. Dr. Lauer responded that a review of trends in the 1980s and 1990s would be interesting. He added that overall priority scores correlate well with reviewers' assessment of the Approach component of the application, but scores of subcomponents are not available for past years.

VII. Connectomics—Brain Mapping at the Level of Synaptic Connections: Promising and Perilous: Dr. Jeff Lichtman

Dr. Lichtman presented his work on mapping the brain at the synaptic connection level. The brain is a unique organ that operates under an organization principle where different parts of the brain do different things—planning in the front, vision in the back, balance in the cerebellum, and breathing in the brain stem. Every other organ system has a cellular motif that explains the normal function of the organ and informs understanding of disease in that organ.

Our understanding of brain function is at a much more primitive level because scientists have not had the capability to see physical abnormalities in brains that aren't working properly. In the cortex, nerve cells have an extraordinarily complicated shape with multiple dendrites coming out of the receptive end of each neuron, and each neuron has an axon that can run centimeters to other parts of the brain, down the spinal cord, or cross hemispheres in the brain. Connectomics is the branch of biotechnology concerned with applying computer-assisted image acquisition techniques and analysis to the structural mapping of neural circuits using high-speed methods.

Dr. Lichtman's work focuses on answering questions such as: How many interneurons contribute to a specific circuit? How does every cell within a class innervate other cells? Answering these questions contributes to understanding the connectional underpinning of human behavior. To understand these phenomena, one must be able to see a higher level of detail.

The behavioral repertoire of humans cannot be attributed to genetics alone; rather, experience modifies the nervous system. Dr. Lichtman displayed maps of wiring in the muscle that wiggles a mouse's ear. He noted the presence of suboptimal, seemingly inefficient wiring, that is, useless loops and premature branching in the organization of nerve connections in a mouse muscle. He also observed that wiring greatly varies between individual mice and changes over time, seeming to indicate that the wiring is a product of development. At birth, a single axon appears to be trying to contact almost every single muscle fiber in a particular muscle, but later in life this same axon has sparse connectivity. More than 90 percent of the synaptic branches in the periphery are eliminated during early post-natal life.

This raised the question: Could this kind of simplification and pruning activity occur over time in the central nervous system? Exploring this possibility would require being able to see all of the connections. Because this is not possible with an electron microscope, members of Dr. Lichtman's team built a machine that ultimately produces a library of automatic, tape-collected ultra-microtome sections of the brain. Unfortunately, image acquisition time using this machine was a problem; it took 100 days at the rate of one terabyte a day to image an area the size of a grain of salt. The team now has acquired a MultiSEM 505, a superfast electron scanning microscope that has 61 parallel electron beams and can accomplish the same work in two days.

One major challenge using the raw image data is that a computer cannot trace connections from one cross-sectional image frame to another. Dr. Lichtman's team has been developing training algorithms to automate image segmentation so that the computer can recognize and color-label each component from frame to frame. The goal is to approach 99 percent accuracy with the automated process.

An extraordinary number of different objects are packed into a tiny piece of brain, and these can be classified as axons (excitatory and inhibitory), glial cells, dendrites (spiny and smooth), astrocytes, etc. One cubic millimeter of cortex contains 1 billion synapses. Looking at a database of the synapses, Dr. Lichtman observed cases where multiple spines of one dendrite were innervated by the same axon in the neocortex. This suggests that particular axons have an affinity for particular dendrites.

Dr. Lichtman concluded by pointing out that his team has succeeded in mapping one-billionth of a mouse brain, which has produced a huge amount of data. The question now is: How can these data be understood? In the last century, scientists had a lot of "profound insights" into how the brain might work, without any supporting data. Now, the scientific community is shifting from this position of pseudo-understanding to having a lot of data and very little understanding.

Discussion

Dr. Tromberg asked whether the brain is a massively redundant system that is designed to keep the human body functioning after a catastrophe. Dr. Lichtman replied that this is a very complicated, dynamic system. His calculations suggest that whatever wiring survives the pruning process must be significant. The remaining axons are doing a lot.

Dr. Smirniotopolous asked if astrocytes are involved in remodeling dendritic spines. Dr. Lichtman stated that there is a large body of literature claiming that the spines constantly turn over, and that is what learning is. However, other studies found that a particular spine was still present in the same place over time. He has an idea that a lot of those objects are stable, which relates somehow to memory. Things learned at a young age are stored so that we do not have to relearn every memory.

Dr. Lee observed that his patients who suffered even a brief electrical shock fare much worse than those who have an amputation. The nervous system seems better able to cope with amputation as opposed to destruction of myelin on the peripheral nerves. He asked whether Dr. Lichtman could explain why this seems to be the case. Dr. Lichtman pointed out that damaged axons grow back in the peripheral nervous system; even in a crush injury, they may grow back via Schwann cells to the same muscle. In some serious injuries, axons grow back profusely but do not reconnect to the correct place.

VIII. Adjournment

The open session of the NACBIB meeting was adjourned at 1:00 p.m.

IX. Closed Session

The grant application review portion of the meeting was closed to the public in accordance with provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2). The closed session was adjourned at 2:15 p.m.

Certification:

We certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.[1]

William Heetderks, M.D., Ph.D.
Acting Executive Secretary
National Advisory Council for Biomedical Imaging and Bioengineering
Acting Director
Office of Research Administration
National Institute of Biomedical Imaging and Bioengineering

Roderic I. Pettigrew, Ph.D., M.D.
Chairperson
National Advisory Council for Biomedical Imaging and Bioengineering
Director
National Institute of Biomedical Imaging and Bioengineering

[1] These minutes will be approved formally by the Council at the next meeting on May 18, 2015, and corrections or notations will be stated in the minutes of that meeting.