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]
May 19, 2006

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 11th meeting on May 19, 2006, at the Marriott Bethesda North Conference Center in Bethesda, MD. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), served as Chairperson.

In accordance with Public Law 92–463, the meeting was open to the public from 8:00 a.m. to 12:00 p.m. for the review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:00 p.m. to 3:00 p.m. for the discussion and consideration of individual grant applications.

Council members present:
Dr. Ronald L. Arenson
Dr. Carlo J. De Luca
Dr. David J. Dzielak
Dr. Robert I. Grossman
Dr. Linda C. Lucas
Dr. Norbert J. Pelc
Dr. Rebecca R. Richards-Kortum
Dr. James A. Zagzebski

Council members absent:
Dr. Don Giddens (Present for closed session *via* teleconference)
Dr. Augustus O. Grant (Present for closed session *via* teleconference)
Dr. Stephen A. Williams
Dr. Frank C. Yin

Ex officio members present:
Dr. Bruce H. Hamilton
Dr. P. Hunter Peckham
Dr. James G. Smirniotopoulus
Dr. Andrew Watkins

[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 have occurred. This procedure only applies to applications that are discussed individually, not to "en bloc" actions.

Ex officio members absent:
Dr. Michael Leavitt
Dr. Vincent L. Vilker
Dr. Elias A. Zerhouni

Executive Secretary:
Dr. Anthony Demsey

Also present:
NIBIB staff present for portions of the meeting:

Ms. Lillian Ashley
Dr. Prabha Atreya
Mr. Angelos Bacas
Dr. Richard Baird
Ms. Sheila Barrett
Ms. Angela Burks
Dr. Zohara Cohen
Ms. Nancy Curling
Ms. Keisha Dent
Ms. Cheryl Fee
Ms. Shirley Finney
Ms. Carol Fitzpatrick
Dr. David George
Ms. Colleen Guay-Broder
Dr. John Haller
Dr. William Heetderks
Ms. Jeanellen Kallevang
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Brenda Korte
Dr. Hector Lopez
Dr. Ying Ma
Dr. Dale Kiesewetter
Dr. Peter Kirchner
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Nicholas Mitrano
Mr. Larry Morton
Mr. Joe Mosimann
Dr. Peter Moy
Mr. Aaron Nicholas
Mr. Long Nguyen
Dr. Roderic I. Pettigrew
Dr. Belinda P. Seto
Ms. Theresa Smith
Ms. Casey Stewart
Dr. Manana Sukhareva
Ms. Florence Turska
Dr. Fei Wang
Ms. Carolyn Williams
Mr. Matt Wise
Ms. Li-Yin Xi
Dr. Yantian Zhang

Other Federal employees present:
Dr. David Brown, Food and Drug Administration
Dr. Mrunal Chapekar, National Institute of Standards and Technology
Dr. Dharam Dhindsa, Center for Scientific Review
Dr. Iacovos Kyprianou, Food and Drug Administration
Dr. Albert Lee, National Institute of Standards and Technology
Dr. Xiang-Ning, Li, Center for Scientific Review
Dr. Weihua Lui, Center for Scientific Review
Dr. Kyle Myers, Food and Drug Administration
Dr. Janet Nelson, Center for Scientific Review
Dr. Ross Shonat, Center for Scientific Review

Dr. Guo Feng Xu, Center for Scientific Review
Dr. Zhiyun Xue, National Library of Medicine

Members of the public present for portions of the meeting:
Ms. Lauren Bildner, Capital Consulting Corporation
Ms. Pat Ford-Roegner, American Institute for Medical and Biological Engineering
Dr. Gary Glover, Stanford University
Ms. Rhonda Goldstein, ORC Macro
Ms. Mariana González del Riego, Rose Li and Associates, Inc.
Ms. Masuko Kaufman, Iri Sangyo Shinbus Press
Ms. Jeanie Kennedy, American Academy of Orthopedic Surgeons
Ms. Amy Lavarola, Rose Li and Associates, Inc.
Ms. Lily McCutchan, National Capital Captioning
Dr. Thomas Meade, Northwestern University
Mr. Ed Nagy, Academy of Radiology Research
Mr. Mark Pak, National Capital Captioning
Dr. William Sansalone, Georgetown University

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey called to order the 11th NACBIB meeting. He reminded attendees that since the morning session of the Council meeting was open to the public, comments about applications should be reserved for the closed afternoon session. Dr. Demsey introduced Dr. Pettigrew, who formally welcomed all participants.

II. Opening Remarks: Dr. Roderic Pettigrew

Dr. Pettigrew opened by welcoming Dr. Hunter Peckham to the NACBIB. The new liaison from the Department of Veterans Affairs (VA), Dr. Peckham is a Donnell Institute Professor of Biomedical Engineering and Orthopaedics at Case Western Reserve University, where he earned his Ph.D. He is also Director of the Functional Electrical Stimulation Center at the Louis Stokes VA Medical Center in Cleveland, OH. Dr. Peckham's research is in rehabilitation engineering and neuroprostheses with a focus on functional restoration of paralyzed upper extremities in individuals with spinal cord injuries.
The May 19, 2006, NACBIB meeting will be the last for Drs. Carlo De Luca, Linda Lucas, Norbert Pelc, and James Zagzebski as they complete 3 years of service. These four Council members hold the distinction of being among the original 12 members of the NACBIB.
Dr. Pettigrew thanked the departing Council members for their service, wisdom, and steadfast participation and offered each a plaque and a letter of appreciation from the Secretary of Health and Human Services, Mr. Michael Leavitt.

III. Director's Report: Dr. Roderic Pettigrew

Dr. Pettigrew summarized activities of the Institute since the January 2006 Council meeting, including the budget outlook, significant events, and scientific highlights and initiatives.

A. NIBIB Budget

The NIBIB fiscal year (FY) 2006 appropriations budget was $296 million; the NIBIB President's Budget for FY 2007 is $294 million. Although this represents a net budgetary decrease of 0.7 percent, relative increases in funding from FY 2006 to FY 2007 are observed in the following areas:

- Pathways to Independence Program: This trans-National Institutes of Health (NIH) program is intended to increase the number of new investigators as well as those who transition into faculty positions (*via* the K99/R00 award mechanism).
- Genes and Environment Initiative: This trans-NIH, genome-wide association study will analyze a large cohort of subjects with a variety of diseases in an effort to correlate genetic variations and environmental impact with common diseases.
- Intramural Budget: The increase in the NIBIB intramural budget will support the recruitment of an Intramural Research Program Scientific Director.
- NIH Roadmap for Medical Research: While funds for the NIH Roadmap account for a significant increase, the increase is not very large in actual dollars.

Dr. Pettigrew addressed concerns among the extramural research community and other NIBIB constituents regarding the Institute's contribution to NIH Roadmap activities, which, some are concerned, detracts from the NIBIB's ability to fund new research grants. Specifically, Dr. Pettigrew pointed out the following:

1. **NIBIB constituents gain from the Institute's investments in trans-NIH research.**
   In FY 2006, the NIBIB contributed approximately $2.7 million to NIH Roadmap efforts. That same year, NIBIB constituents were awarded 16 grants, in total, approximately $9.5 million. A return also was seen in the Institute's investment in the NIH Blueprint for Neuroscience Research, to which NIBIB contributed $190,000 in FY 2006, and obtained a return of $4.5 million in funding.

2. **The NIH contribution to the Roadmap is relatively small.**
   In FY 2005, the Roadmap accounted for only 0.8 percent of the total NIH budget. Roadmap funding will increase to 1.2 percent of the total NIH budget in FY 2006 and peak at 1.7 percent in FY 2007 and 2008.

3. **NIH Roadmap activities eventually will migrate into individual Institutes.**
   The NIH Roadmap is intended to accelerate critical research efforts that address major problems not easily addressed by any single Institute or groups of Institutes. After being initiated through the Roadmap mechanism, these initiatives are expected to become part of other Institutes' portfolios. The Molecular Imaging Initiative, for instance, will move into the NIBIB portfolio after FY 2009.

4. **Other factors affect the NIBIB's ability to fund extramural grants.**
   Three factors unrelated to NIH Roadmap funding have driven the NIBIB's ability to fund extramural grants: (1) Large capacity building throughout U.S. research institutions and dramatic increase in number of tenure-track faculty, which has increased the pool of

potential grant applicants; (2) large increase in the number of grant applicants and applications, particularly after 2003, the last year of the doubling of the NIH budget; and (3) appropriations that have been below the inflation level since after 2003.

5. **The NIBIB strives to reserve one-fourth of its annual appropriations for new grant awards.**
   While approximately three-fourths of the NIBIB's annual funds support continuing grants, approximately one-fourth of funds are uncommitted. Achieving the balance between committed and uncommitted funds represents a challenge and requires careful attention to the combination of size and duration of awards.

B. NIH-Wide Events

Multiple Principal Investigator (PI) Awards: A new effort to allow more than one PI on individual NIH research awards will encourage multidisciplinary efforts and collaboration to maximize the potential of team science. The number of PIs permitted on a multiple-PI grant will not be limited, and while only one PI can be designated as the "Contact PI" or NIH liaison, this role may be rotated among PIs annually. Phase-in of the program is under way and will continue through 2008 when the program is expected to be fully operational. Among the six program announcements (PAs) that will pilot the multi-PI program is one NIBIB program announcement on regenerative medicine, for which Dr. Fei Wang will serve as Program Director.

NIH Roadmap Nominations: The NIH is soliciting ideas for new trans-NIH initiatives from the extramural research community as the Roadmap moves into a new phase. The nomination process will consist of three phases. Phase 1 will occur May to June 2006 and will involve collecting and vetting nominations. Phase 2 will occur in July 2006 and will include five consultation meetings with the goal of ranking nominations. Phase 3 will involve reviewing summary data derived from Phase 2 to identify winning nominations.

C. NIBIB-Specific Activities

Funding for High-Risk, High-Impact Research: The NIBIB is launching a new strategy for supporting high-risk, high-impact research. The goal of the strategy is to identify and fund two or more highly innovative R01 applications annually. Applications must score well yet miss the NIBIB payline. This strategy will help address longstanding concerns among the extramural research community that the peer review process favors more conservative research endeavors.

Regional Grantsmanship Seminar Series: To help improve the success rate of grant applicants, the NIBIB is conducting a Regional Grantsmanship Seminar Series. Three grantsmanship seminars were held between 2005 and spring 2006—one each in Troy, NY; Washington, DC; and Research Triangle Park, NC. One additional seminar is scheduled for fall 2006 in Houston, TX. Information on hosting a seminar is available at www.nibib.nih.gov/nibib/File/Funding/NIBIB_Grantsmanshiphost_logistics.pdf.

Scientific Workshops Cosponsored by the NIBIB: Among significant scientific workshops held since the January 2006 Council meeting are the following:

- *Improving Health Care Accessibility Through Point-of-Care Technologies*: Held in Arlington, VA, on April 11 and 12, 2006, this workshop will serve as the basis for issuance of a request for applications (RFA) to be funded by the NIBIB in FY 2007. The RFA will focus on technologies that will bring diagnostic capabilities to clinical settings.
- *Imaging the Pancreatic Beta Cell in Health and Disease*: Held in Washington, DC, on April 24 and 25, 2006, this workshop explored progress in imaging of the pancreatic islet cell mass to assess its functionality in health and disease. The NIBIB will continue in this effort, as it underscores an area of particular interest to the Institute—imaging microcellular populations and cell populations specific to disease processes.

Quantum Projects Exploratory Grants: The response from the extramural research community to the Quantum Projects Exploratory Grants RFA issued in November 2005 has been strong. It is expected that the review panel will convene in July 2006. Awards will be issued in fall 2006.

The NIBIB Web Site: The NIBIB Web site won an Award of Distinction from *The Communicator Awards,* an international competition recognizing outstanding work in the communication field. There were more than 5,000 entries from the United States and abroad in the 2006 competition. The visually appealing and user-friendly NIBIB Web site is the result of a redesign conducted in 2005 headed by Ms. Colleen Guay-Broader, Director of the NIBIB Office of Science Policy and Public Liaison.

Recent additions to the site include a video gallery and a subsite on the Multi-Scale Modeling Initiative. The latter is headed by Dr. Grace Peng, who was featured in an article in the spring 2006 issue of *Biomedical Computation Review* on the gender gap in computer sciences.

D. Scientific Initiatives and Highlights

Dr. Pettigrew highlighted the recent work of NIBIB grantees in multiple subject areas.

Personalized Coronary Angiography: A joint effort between the NIBIB and the Food and Drug Administration (FDA) supports a laboratory that assesses medical imaging science and technologies. Among the funded FDA fellows is **Dr. Jake Kyprianou**, who is examining the physical parameters of a computer tomography system for use in angiography. The goal of this research is to develop the technology for application in a personalized fashion by modifying a model based on patient-specific data, optimizing the parameters, and then conducting an examination that provides the best image quality relative to radiation dose. For his presentation of this work, Dr. Kyprianou received a best poster award at the February 2006 International Society for Optical Engineering Medical Imaging Symposium.

Research on the Brain-Computer Interface: **Dr. Jonothan Wolpaw**, Wadsworth Center, New York State Department of Health, conducts research on the brain-computer interface. He has developed an algorithm that takes the array of signals from spatial localizations on a skullcap worn by a user, translates those signals into instructions in terms of the user's intent relative to his or her thinking, and applies those instructions to allow the user to communicate with a computer. Dr. Wolpaw's research currently is being applied on a patient with amyotrophic lateral sclerosis.

Parallel Magnetic Resonance Imaging: **Dr. Daniel Sodickson**, Harvard University, received the highest honor bestowed upon a scientist by the International Society for Magnetic Resonance in Medicine (ISMRM)—the ISMRM Gold Medal. This award acknowledges Dr. Sodickson's groundbreaking research on parallel imaging, which increases the speed at which magnetic resonance (MR) images can be obtained. Taking advantage of spatial variations in signals when using multiple coils, Dr. Sodickson generated multiple signals with each MR experiment and thereby reduced the time to acquire these data by twelvefold.

IV. Review of Regulations, Policies, and Procedures: Dr. Anthony Demsey

A. Council Regulations, Policies, and Procedures

Dr. Demsey summarized elements of the Government in the Sunshine Act and the Federal Advisory Committee Act that govern all Advisory Council meetings. These Acts require the Department of Health and Human Services to open Advisory Council meetings to the public except when proprietary or personal information is discussed. To comply with these regulations, the NACBIB meeting is open to the public except for the review of grant applications.

In briefing Council members on the guidelines for conflicts of interest and confidentiality issues, Dr. Demsey emphasized the importance of maintaining confidentiality in all settings, formal and informal. Council members were given examples of when these guidelines should be applied and were offered the opportunity to ask questions to clarify any areas of uncertainty.

Attendees were also reminded that for the duration of the meeting, they were special government employees and bound by Federal standards of conduct, and therefore not allowed to engage in lobbying activities.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for September 15, 2006. Dr. Demsey asked Council members to inform him of major conflicts with any other scheduled upcoming meeting dates.

C. Approval of the January 25, 2006, NACBIB Meeting Minutes

A motion was entertained to approve the minutes of the January 25, 2006, NACBIB meeting. Dr. Demsey requested minor changes to the meeting list of participants. The minutes were approved unanimously with these modifications.

D. Other Announcements

Dr. Demsey welcomed three individuals representing scientific association constituencies: Ms. Jeanie Kennedy, Manager, Regulatory Affairs for the American Academy of Orthopaedic Surgeons and Ms. Patricia Ford-Roegner, Executive Director of the American Institute for Biomedical and Biological Engineering, and Mr. Ed Nagy, Academy of Radiology Research.

V. Report of the Strategic Plan Implementation Working Group Meeting: Dr. Norbert Pelc

During the May 18, 2006, NACBIB Strategic Plan Implementation Working Group meeting, members reviewed the NIBIB strategic plan and confirmed that it remains an accurate guidance document for the Institute. Furthermore, all concurred that given current budget pressures, the manner in which limited resources are deployed will be critical.

A. Fostering the Careers of Early-Stage Investigators

The group discussed an area of critical concern—the development of the next generation of researchers in biomedical imaging and bioengineering. All members endorsed a continued investment in training. The group then turned its attention to early-stage investigators, who require more robust support than seasoned investigators to launch careers as competitive, independent researchers. They applauded the NIH's new K99/R00 mechanism and recognized as a positive step the 5-percentage-point advantage in the funding of R01s awarded to new investigators. However, all agreed that a mechanism focused specifically on the early-stage investigator is important. While the R21 mechanism currently is being used in this capacity, it is not necessarily the best mechanism for supporting new investigators. The group therefore recommended that the NIBIB consider developing a program targeted specifically to early-stage investigators. Key features of such a program should include initial awards of significant duration (4 to 5 years) to allow new investigators to firmly establish themselves.

Discussion around what constitutes a "new investigator" ensued. Some argued that only early-stage investigators should be targeted in the efforts described above; others argued that investigators who may be more seasoned but whom the NIH has never funded should benefit from such support as well.

B. Supporting Team Science

Working Group members agreed that the NIBIB's balance of funding team science *versus* individual investigator grants is appropriate. However, they emphasized that in biomedical imaging and bioengineering, team science is of critical importance. One mechanism by which the NIBIB could enhance its support of team science is *via* public-private partnerships. Specifically, the subcommittee recommended public-private funding of early-stage research that industry would not otherwise pursue on its own. A well-tuned mechanism for funding team science is the Bioengineering Research Partnership (BRP) program. The group recommended that the NIBIB maintain the number of BRP awards, given the current budget climate. Some members also recommended that the NIBIB make it less difficult to exceed the cap on BRP awards because this mechanism is one of few that can fund particularly large research grants. In addition, the group recommended that the NIBIB consider BRP awards for funding at all cycles rather than only once a year.

C. Administrative Issues

More than a year ago, NIBIB staff examined the Institute's portfolio of grants and categorized them into scientific priority areas. The group felt that this exercise was important and that it

should be repeated with the involvement of Working Group members to ensure that the scientific priority areas identified are inclusive of all areas of biomedical engineering and medical imaging that require attention.

Since two members will be departing the Strategic Plan Implementation Working Group as their terms expire this year, the remaining members agreed to postpone the selection of a new chair until new members are appointed.

VI. Report of the Training and Career Development Working Group Meeting: Dr. Linda Lucas

Although the Training and Career Development Working Group includes six Council members, only Drs. Lucas and Rebecca Richards-Kortum were present for a meeting held May 18, 2006. Dr. Richard Baird, Director of the Division of Interdisciplinary Training at the NIBIB, also joined the group.

Dr. Lucas opened by emphasizing the importance of both NACBIB Working Groups working together because of the overlap of issues in training and career development and strategic planning, and because of the impact each group's decisions will have on NIBIB resources.

While members of the Training and Career Development Working Group discussed a variety of topics, the bulk of the discussion revolved around training needs for new investigators—that is, early-career investigators and new faculty members without research funding. It was agreed that early and adequate training that helps new investigators secure their first grants is essential. In the case of a new faculty member for example, this funding often results in an institution increasing mentoring, financial, and other support to that individual. Group members considered the R21 as a mechanism for supporting new investigators but concluded that this mechanism is best dedicated to funding innovative, high-risk research.

Other topics addressed by the group included the following:

- Are current postdoctoral training programs serving their purpose?
- What types of midcareer training activities should the NIBIB support?
- What can be learned from the best practices of other agencies' programs, such as the National Science Foundation (NSF) Integrative Graduate Education and Research Traineeship Program?
- Could incentives for training be incorporated into the T32 mechanism?

These areas were discussed extensively although no consensus was reached.

In closing, Dr. Lucas reminded the NACBIB that faculty members typically have appointments across multiple disciplines such as engineering, basic health sciences, and clinical programs. Therefore, in considering NIBIB goals, there needs to be sensitivity to this continuum to best serve the biomedical imaging and bioengineering community. She also suggested that the Training and Career Development Working Group would benefit from the involvement of a Council member representing clinical programs.

VII. Update on Current NIBIB Training Activities: Dr. Richard Baird

Dr. Baird provided an update on current training activities and shared his vision for the Institute training portfolio. He opened his presentation by describing current efforts to enhance NIBIB training opportunities, which include the following:

- Redirecting the program balance and reducing institutional training programs' growth;
- Encouraging a combination of smaller, focused and larger, broad-based programs;
- Redirecting career development awards to early-career investigators, especially those with clinical or quantitative backgrounds, and to midcareer investigators with mentoring experience;
- Redirecting individual fellowships (not minority fellowships) to a small number of outstanding investigators; and
- Anticipating the future entry of Howard Hughes Medical Institute-NIBIB programs into the training portfolio.

Several ongoing activities and potential efforts to further enhance training are described below.

A. NIBIB Training Needs Assessment

With support from the Opinion Research Company (ORC) Macro, the NIBIB is assessing the number of researchers in biomedical imaging and bioengineering, their distribution across employment sectors, the number initially trained in other disciplines, sources of support and paths to success, and proportion of underrepresented populations. The initial assessment included interviews with academic, industry, and government leaders, and statistical analysis of training data from the NIH and other agencies. Recommendations made by interviewees included filling the void left by the loss of the Whitaker Foundation Young Investigators' Award, emulating the NSF Research Experiences for Undergraduates Program, and supporting curriculum development, especially for interdisciplinary programs. Interviewees were also asked the following questions:

- What is the appropriate combination of academic and industrial training?
- Within the academic setting, what is the appropriate combination of institutional and individual training?
- What is the interaction between training and research? Specifically, where do NIBIB-funded trainees go, and how many NIBIB-funded trainees seek NIBIB research support?

Currently, ORC Macro is mining progress report data and creating a tracking data base of predoctoral, postdoctoral, and early-career investigators. The next steps in the assessment process include conducting a post-assessment workshop with interviewees and Council members, statistically evaluating training and career development mechanisms with NIH set-aside funds, and participating in the National Research Council's National Research Service Award (NRSA) assessment program.

B. T32 Grantee Meeting

A Training (T32) Program Directors' meeting is scheduled for June 16, 2006. Upcoming changes to the T32 program and individual programs' successes and challenges will be discussed, and the open questions listed above will be presented to the audience for feedback. Also on the agenda are a keynote address, panel discussions, and two breakout sessions—one for program directors and one for trainees.

C. Potential NIBIB Training Initiatives

Training initiatives currently under consideration include a new-investigator initiative, public-private training partnerships, Center-based training, and minority training.

D. NIH Tuition Policy Update

Under the current formula, the NIH reimburses 100 percent of requested tuition, fees, and health insurance (T/F/I) expenditures up to $3,000 and 60 percent of costs above $3,000, per trainee. However, costs in these categories have been rising at a rate of 7 to 11 percent per year. Continuation of this trend may result in a significant annual decrease in the number of NRSA training positions and fewer programs supported by T32 awards, thus hindering the development of research capacity. As a result, in November 2005, the NIH convened a Town Hall meeting to gather feedback on three approaches to address rising T/F/I costs: (1) Capping the tuition formula, (2) fixing tuition payment, or (3) keeping the existing formula but reducing the number of awards. Based on feedback from meeting participants, the NIH drafted a new policy for reimbursement of costs associated with T/F/I. The draft policy is available for public comment until June 2, 2006, and includes the recommendations:

Predoctoral Recommendations:

- Cap current formula at $16,000 (single-degree programs) or $21,000 (dual-degree programs).
- Allow $4,200 per trainee (a $2,000 increase) for health insurance and training-related expenses.

Postdoctoral Recommendations:

- Cap current formula at $4,500 (non-degree programs) or $16,000 (degree-granting programs).
- Allow $7,850 per trainee (a $4,000 increase) for health insurance and training-related expenses.

The new policy, which will decelerate the loss of training positions, will apply to all NRSAs beginning in FY 2007. The policy will be revisited biennially for competing awards.

E. NIH Pathway to Independence Career Transition Award Update

The first receipt date for Pathway to Independence Awards, also known as K99/R00 awards, was April 7, 2006, and the peer review is scheduled for June 19. The second receipt date for Pathway

to Independence Awards is June 1, 2006. Thus far, major eligibility issues include visa matters, applicants with more than 5 years of postdoctoral training, applications proposing less than 1 year for the K99 phase, and applicants with previous or promised faculty positions.

F. Residency Supplement Update

The Residency Supplement Program completed its third round in May 2005. Of the 12 applications received in that round, the NIBIB will fund four. The program has been very successful and therefore will be reissued with new receipt dates as follows: October 21, 2006; February 21, 2007; and June 21, 2007.

G. Discussion

A Council member inquired whether the Training for New Interdisciplinary Research Workforce (T90) award mechanism would be expanded for use outside of the NIH Roadmap. Dr. Baird responded that this mechanism is not being used currently beyond the Roadmap, although it may be expanded in the future. In the meantime, since the mechanism currently available to individual Institutes (i.e., the T32 award) does not support curriculum development, the NIBIB could investigate curriculum development programs used by other NIH Institutes and Centers.

There was also discussion among Council members about how best to support new investigators. One Council member suggested using incentives in multi-investigator grants and BRPs to encourage the inclusion of new investigators in those grants. Some, however, argued that individual awards are essential for early-career investigators. For new faculty, for instance, tenure often depends on such an award. Other Council members commented that while individual awards are important at the postdoctoral level, institutional grants are sufficient at the predoctoral stage. Two central recommendations emanated from the discussion:

- The NIH should consider how to increase the distinction of NIH predoctoral fellowships, which currently do not have the same prestige as, for instance, Whitaker Foundation and NSF fellowships. The apparent lack of distinction of NIH predoctoral fellowships is due, in part, to a concern that mentors may be involved heavily in writing the extensive research plan required of applicants.
- The NIH should create an award that is better suited to helping investigators transition from a K- to an R-series mechanism. Such an award would have milestones along a 4- to 5-year timetable to encourage early-career investigators to graduate to an R01 award.

While the NIH implemented a policy 5 years ago that allows K-award grantees to apply for and receive independent grant awards, some Council members suggested that early-career investigators require further support to transition successfully to independent careers. Discussion of the Mentored Patient-Oriented Research Career Development Award (K23) mechanism in particular ensued. One Council member found it to be a useful mechanism despite its limitations; another said that the expectations, financial structure, and academic roadmap of the K23 were not appropriate.

VIII. Staff Presentation: Optical Imaging and Imaging Agent Development: Dr. Yantian Zhang

Dr. Zhang described developments in two NIBIB program areas—optical imaging and imaging agent development, both of which help realize the NIBIB's goal to spearhead the development and application of emerging and breakthrough biomedical technologies that will improve public health. In the optical imaging program, there are currently approximately 80 grants totaling $20 million in funding, and there are approximately 50 grants and $17 million in funding dedicated to the imaging agent development program. Further information on each of these programs and two strategic plan initiatives that are currently under development within the NIBIB were presented.

A. The Optical Imaging Program

Optical imaging is not a single imaging modality but includes diverse imaging technologies based on different physical principles. Examples include fluorescence/bioluminescence imaging, confocal and multiphoton microscopy, and optical microscopy/spectroscopy. The common theme uniting these diverse imaging technologies is that most of them, except scanning probe microscopy, operate in or around the visible range of the electromagnetic spectrum. Another characteristic of optical imaging technologies is their broad range of application, from physics and chemistry to biology and medicine. Examples of currently supported research in this program are described below.

Assessment of Coronary Plaque Collagen With Polarization-sensitive Optical Coherence Tomography (PS-OCT)
Dr. Mark Brezinski, Harvard University, and collaborators are using PS-OCT to identify vulnerable coronary plaques by examining the collagen in those structures. The goal of this research is to further develop PS-OCT technology to allow researchers to identify lesions predisposed to progress to unstable angina, which potentially leads to myocardial infarction. The investigators plan to develop an endoscopic approach and, ultimately, to use PS-OCT as a predictive clinical tool.

Development and Application of Ultrashort Femtosecond Laser
In one application of ultrashort femtosecond laser technology, **Dr. David Kleinfeld**, University of California, San Diego, and colleagues are using high-fluence, short-laser pulses to clot surface cortical vessels individually in a mouse model to study how brain vasculature responds to such a clotting event. Thus far, the investigators have found that a single clotting event has a significant effect in downstream flow, impairing flow to 10 percent of its before-clotting value and suggesting that such a clotting event could lead to local ischemia.

Fluorescence Molecular Imaging
Dr. Vasilis Ntziachristos, Massachusetts General Hospital, and collaborators are using fluorescence molecular imaging to study mouse models of inflammation. Specifically, the investigators developed a fluorescent optical imaging probe that is sensitive to cathepsins, which is upregulated significantly during inflammation and thereby is able to pinpoint the site of inflammation. Dr. Ntziachristos and other research groups such as the research group led by **Dr.**

Ge Wang, University of Iowa, have also attempted to reconstruct 3D distributions of fluorescence or bioluminescence signal sources using photon transport modeling.

B. The Imaging Agent Development Program

The purpose of imaging is to extract, spatially and temporally, resolved information about specific biological activities, processes, and functions beyond anatomy and structure. Use of contrast media is a means to facilitate imaging of specific biological processes and functions. They are applied to imaging apoptosis, inflammation, cell tracking, imaging brain metabolism, imaging neurotransmitters, etc. Among the specific aims of the NIBIB Imaging Agent Development Program are the following:

- Develop innovative imaging contrast agents and contrast mechanisms;
- Develop activatable, targeted molecular imaging probes;
- Conduct imaging agent toxicity and biocompatibility research; and
- Conduct imaging agent applications research.

Examples of current research in this program include the following:

Quantum Dots

There has been much discussion in the scientific community about quantum dots and whether they serve well as contrast agents. In essence, quantum dots are semiconductor nanocrystals and, as such, they possess superior optical properties. Their excitation spectrum is broad, and their emission spectrum is both narrow and symmetric. As a result, quantum dots allow for better control of emission peaks and as represented by the work of **Dr. Shimon Weiss**, University of California, Los Angeles (UCLA), it is an area of emphasis for the NIBIB Imaging Agent Development Program.

Transgene Reporter for *In Vivo* Magnetic Resonance Imaging (MRI)

Another area of exciting research is in the development of molecular imaging approaches using more commonly available imaging modalities such as MRI. In one example, **Dr. Eric Ahrens**, Carnegie Mellon University, and colleagues are attempting to develop a transgene reporter for *in vivo* MRI by studying gene expression. To this end, the investigators created, as an MR reporter, a gene construct using an adenovirus vector. They found that cells transfected by this adenoviral vector accumulate endogenous iron from the organism, making them super paramagnetic and thereby dramatically increasing their relaxivity. This research is novel in that it allows the imaging of gene expression using a clinically available model.

Prostate-Specific Membrane Antigen (PSMA)-based Gene Reporter-Probe System

Dr. Martin Pomper, Johns Hopkins University, and collaborators are modifying a reporter-probe system originally developed at UCLA so that research can be applied more readily to humans. In a mouse study, investigators transfected tumor cells with a PSMA-based gene reporter. They then developed probes (positron emission tomography, optical imaging, and MRI) specifically for the PSMA-based gene report, thereby enhancing the tumor in *in vivo* imaging studies. There are high hopes for translating this probe-reporter system into human applications.

C. Strategic Plan Implementation

Two initiatives currently under development will strengthen and expand NIBIB efforts in optical imaging and imaging agent development.

Development of Bioactivatable Agents
The primary goal of this initiative is to support fundamental research, development, and validation of multimodal imaging agents with bioactivatable imaging contrast and/or therapeutic effects. A prime example of such research is the work of **Dr. Thomas Meade**, Northwestern University, and colleagues, who have developed gadolinium-based MRI contrast agents that are activated by β-galactosidase, which release a sugar group attached to the gadolinium. Using such an approach, MRI can be used to visualize cellular-level enzymatic events with resolutions down to 12 μm (*Nature Biotechnology,* 2000).

Translation of Optical Imaging to *In Vivo* Preclinical and Clinical Applications
The primary goal of this initiative is to stimulate translational research and development of optical imaging techniques for preclinical and clinical applications and to accelerate the delivery of clinical benefits of optical imaging, microscopy, and spectroscopy. NIBIB has held two discussion sessions earlier this year, at the OSA Biomedical Optics Topical meeting and at the 2006 ISBI meeting, dedicated to encouraging translational research and development of optical imaging for preclinical and clinical applications. In the area of photo-acoustic imaging, research is mainly led by three groups. Primary among them is an NIBIB grantee **Dr. Lihong Wang**, from the Texas A&M University. Dr. Wang is developing a photo-acoustic imaging approach to image microvasculature. This research combines the advantage of optical, high-resolution imaging with the in-depth penetration of ultrasound. The primary goal of this initiative is to encourage and stimulate translational research of this and other technological developments in optical imaging towards clinical applications. In addition to the two meeting sessions described above, a meeting session on this topic will be held at the NIH Optical Imaging Workshop in September 2006.

In conclusion, Dr. Zhang stated that there is currently much excitement about optical imaging and imaging agent development, both of which potentially have a wide range of impacts. However, a host of challenges remain. For instance, depth of penetration remains a major concern in optical imaging, and toxicity studies present obstacles in imaging agent development. Steps to address these and other challenges faced in these NIBIB program areas include the following:

- Providing focused support in critical areas;
- Collaborating within and outside of the NIBIB and the NIH, public-private funding agencies, and industry; and
- Supporting translational research to accelerate the delivery of clinical benefits.

IX. Scientific Presentation—The Chemistry of Biological Molecular Imaging: Dr. Meade

Dr. Thomas Meade is Eileen M. Foell Professor of Chemistry, Biochemistry, and Molecular and Cell Biology, Neurobiology and Physiology, and Radiology at Northwestern University. His revolutionary research focuses on coordination chemistry and its application to bioinorganic problems that include biomolecular imaging, electron transfer processes, and the development of biosensors for the detection of DNA and proteins. In his presentation, Dr. Meade discussed recent work on cell tracking in the central nervous system, delivery systems, biological activation of contrast agents, and novel magnetic resonance (MR) contrast agents that are biochemically activated *in vivo* to monitor gene expression.

Dr. Meade opened his presentation by emphasizing the pivotal role that chemistry plays among the fields of clinical radiology, molecular imaging, and molecular biology in the development of multimodal probes. He added that to achieve scientific advances in these research areas, a multidisciplinary approach is essential.

Dr. Meade then addressed current clinical and laboratory imaging modalities, none of which can overcome all challenges in the field. In the case of MRI, challenges include limited probe sensitivity and resolution. Despite challenges, progress has been made in these areas. MRI's chief capability consists of adding spatial and temporal domains to experiments that no other technique can offer. Being able to observe a live animal over time is crucial to the understanding of developmental and molecular biological processes. As an example, Dr. Meade described a collaboration with Drs. Scott Frazer and Russ Jacobs at the California Institute of Technology, where MRI was used to determine whether developmental and molecular biological events can be correlated with gene expression profiling. Four agents were injected into a mouse embryo (in the neural notochord, heart, liver, and telencephalon), and at high field strengths, high-resolution, time-resolved images allowed the mapping of cells to their lineage.

Historical Overview of Probe Development

Probes used across four imaging modalities—positron emission tomography (PET), computed tomography, MRI, and ultrasound—fall into one of two categories: Injectable agents and genetically encoded reporters (e.g., green fluorescent protein and luciferases). Over the last 10 years, significant advances have been made in the development of probes for all four modalities, and many of them have transitioned into the clinic. However, multimodal contrast agents (i.e., probes that coregister in more than one modality) encompassing the sensitivities of PET and T2 agents, optical fluorescence, and the functionality of a T1 agent remain to be developed to correlate data with developmental events. Dr. Meade described his early accomplishments to improve MR contrast agents, then stressed that synthetic chemical techniques could be used to develop imaging agents not only to track anatomical features but also to monitor gene expression, cell signaling, and therapies.

Improving MR Contrast Agents—Developing Better Agents Through Chemistry

Detecting and characterizing the tissue of interest (i.e., contrast) is the most essential feature of imaging. MR contrast is traditionally based on density of protons and the "relaxation" parameters (T1, T2) of spins, which are affected by their local environment. T1 agents shorten the T1 relaxation, causing faster recovery of the magnetization signal. They are typically used to

generate positive (bright) contrast. Gadolinium is the most common T1 agent. T2 agents shorten T2 relaxation, causing faster dephasing of the signal. They are typically used to generate negative (dark) contrast. Iron-based agents are most common in this category.

Challenges in T1 probe development include increasing brightness, achieving targeted delivery, and developing bioactivated probes to provide information on enzyme activity, gene expression, and secondary messengers. Altogether this represents a coordination chemistry problem.

A previous approach to studying cell patterning consisted of decorating a polymer with multiple gadolinium agents to amplify the signal. Taking this approach into a new era, Dr. Meade, in collaborations with Dr. Jack Kessler of Northwestern University and Dr. Michael Modo of King's College, London, has labeled neural stem cells with T1 contrast agents to track neuroregeneration. To achieve this, a stroke was induced in a rat, and labeled agents were injected a day later. Stem cells were tracked over 2 weeks as they migrated from one hemisphere to the other, where neuroregeneration was initiated. It was observed that, regardless of where stem cells were injected, the migration invariably followed the shortest path and lasted 2 weeks. Migration was observed at 4.7 Tesla and 200 μm. For validation purposes, optical imaging was used during histology to observe stem cells that migrated to the infarct area at a single-cell resolution; approximately 20 percent of the cells differentiated prior to migration. The power of multimodal agents was exemplified in this study as two sets of data were coregistered using MRI and optical imaging for validation purposes.

Unlike current T1 agents, T2 agents are highly sensitive and can be targeted. A translational example of these particles resides in fate-mapping beta islet transplantation. In collaboration with Dr. Dixon Kauffman, a Northwestern Memorial Hospital transplant surgeon, beta islets from cadavers were collected to convert part of the liver into a pancreas. Multimodal agents were used to label beta islets and track them over time. Since the generation of T1 agents used was not bright enough to track over a month's period, a T2 multimodal agent with an iron core and an optical fluorochrome was used instead. Optical images yielded high resolution. When transplanted into the kidney capsules of a mouse, the cells were tracked over 6 months.

To overcome disadvantages of T2 agents, Dr. Meade's laboratory attempted to make a bright T1 multimodal agent exhibiting limited rotational correlation time while simultaneously amplifying the MR signal. To accomplish this, hydrogen bonding domains were introduced into labeled peptides to facilitate self-assembly and restrict bond rotation. The end result was a peptoid—a peptide where the functional group has been shifted from the carbon to the nitrogen—of 7,000 molecular weight that is functional with any imaging modality. The relaxivity of the peptoid approximated that of T2 agents allowing cell tracking even after 100 hours.

Once bright multimodal agents had been developed, the focus turned to targeted delivery. To this end, eight arginine units were added to a classic, clinically approved contrast agent.
X-ray fluorescence confirmed that the agent selectively entered mouse fibroblasts. In addition, it was possible to track the translocation of the gadolinium contrast agent into the cell and through cell differentiation and to determine the concentration of the contrast agent in the cell. An alternate delivery system for specific targeting involved the use of the antiprogestin RU486. Labeled RU486 was shown to cross cell membranes selectively. Similarly, labeled stilbene, an

agent reported by H.F. Kung, University of Pennsylvania, and collaborators to carry PET agents across the blood-brain barrier (*Nuclear Medicine and Biology*, 2003), was injected in the tail vein of a mouse that had amyloid plaque formations associated with Alzheimer's disease. Again, it was shown that the contrast agent crossed the blood-brain barrier and irreversibly labeled the amyloid plaques.

Multifunctional MR Imaging Probes

Based on the lessons learned from cell and lineage migration, targeted delivery, and membrane translocation studies, Dr. Meade's laboratory designed MR contrast agents biochemically activated within the cell to monitor gene expression. In this case, a chelator occupies eight of the nine coordination sites on a gadolinium contrast ion while a galactopyranose residue caps off the remaining coordination site. In this water-inaccessible configuration, the contrast agent is "inactive;" it does not affect the T1 times of MRI images. However, the agent is turned on when β-galactosidase enzymatically cleaves the galactopyranose from the coordination site. A water molecule almost immediately occupies the site, thereby changing its magnetic susceptibility and T1 relaxivity and charging the particle so it is trapped inside the cells. β-galactosidase is an enzyme manufactured by the gene lac-Z plasmid, a common marker gene. The presence of β-galactosidase means the lac-Z gene in those cells is turned on. Consequently, the "turned-on" agent lights up the cells where gene therapy is expressed. To test the functionality of this system, the contrast agent was introduced into both sides of a frog embryo. The lac-Z plasmid was inserted in only one side. Ninety hours later, the agent was detected on one side of the tadpole exclusively. Thus it was shown that gene expression could be tracked *via* an enzyme reporter system.

Other enzymes are being harnessed to help clinicians visualize gene expression and physiological processes in patients. These enzymes include kinases, glucoronidases, metalloproteinases, caspases, and cathepsins, each of which can act on a different metabolite tethered to the contrast agent to indicate the expression of disease-specific genes or the delivery of drugs.

Merging Diagnostics and Therapeutics

The next question addressed by Dr. Meade's laboratory was whether the same strategies mentioned above could be used to merge diagnostics and therapeutics to create a "theragnostic" To this end, doxyrubicin, a commonly used therapeutic, was chosen due to its large size. A macrocyclic gadolinium complex was synthesized with a targeting domain, which could correspond to an arginine, cell surface receptor, or alternate molecule. The drug then was introduced, which covalently attached to the macrocycle. Together, the gadolinium and drug saturated blocking water molecules. Because the two are covalently attached, the agent is silent and the drug is inactive. When a bond of choice is clipped, both the agent and the drug are turned on simultaneously. Using MRI, it was shown that the delivery of doxyrubicin could be targeted and its efficacy monitored in real time. Whether the strategy of wrapping a prodrug and an agent that can be activated into one molecule can be reproduced with other drugs remains to be determined.

Secondary Messengers and Reversible Agents

Dr. Meade presented an example of a secondary messenger and the brain imaging that can be achieved. In this example, a calcium binding domain was added to two contrast agents to make a symmetrical, internally reversible molecule. In the absence of calcium, gadolinium was sterically blocked by carboxylic acids weakly associated with it. In the presence of calcium, the gadolinium becomes accessible, and when calcium binds to the contrast agent, both gadolinium units are turned on. Similarly, when calcium concentrations decrease below a threshold, the contrast agent is turned off.

Although the above strategy was proven, attempts to transport the contrast agent through the blood-brain barrier were not successful. Therefore, stilbene currently is being added to the contrast agent to transport it into the brain. The synthesis involved is extensive, however, and therefore remains to be completed. In the meantime, to determine whether the contrast agent worked in the brain, it was introduced into a mouse through a skull perforation. When the mouse's left whisker barrel was tickled, MRI showed that the calcium-bound agent was turned on mapping calcium excitable cells, indicating that the contrast agent was indeed effective.

Conclusion

New classes of magnetic resonance contrast agents have been developed in the past decade that represent a substantial leap in the type of information that can be derived from imaging experiments; nevertheless, much remains to be accomplished. In closing, Dr. Meade emphasized that the role of chemistry coupled with the clinical and radiological sciences and molecular biology will continue to drive the development of new tools that will make a significant impact on diagnostic radiology.

Discussion

In response to an inquiry by a Council member, Dr. Meade clarified that translocation molecules are able to remove contrast agents from the cell. However, adding a disulfide bond between molecules locks the agent inside the cell.

In response to a question on stilbene's specificity, Dr. Meade acknowledged the need to understand stilbene's binding mechanism and announced that a new collaboration had been established with cellular biologists for this purpose.

X. Adjournment

The meeting was closed for review of applications at 12:00 p.m.

XI. Closed Session

This portion of the meeting, involving grant application review, was closed to the public in accordance with the provisions set forth in Section 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).

XII. Certification

We certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.[2]

_____

Anthony Demsey, Ph.D.
Executive Secretary,
National Advisory Council for Biomedical Imaging and Bioengineering
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

[2] These minutes will be approved formally by the Council at the next meeting on September 15, 2006, and corrections or notations will be stated in the minutes of that meeting.