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 25, 2006

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 10th meeting on January 25, 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 12:30 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 4:30 p.m. for the discussion and consideration of individual grant applications.

Council members present:
Dr. Carlo J. De Luca
Dr. David J. Dzielak
Dr. Don Giddens
Dr. Augustus O. Grant
Dr. Linda C. Lucas
Dr. Norbert J. Pelc
Dr. Rebecca R. Richards-Kortum
Dr. Frank C. Yin
Dr. James A. Zagzebski

Council members absent:
Dr. Ronald L. Arenson
Dr. Robert I. Grossman (Present for closed session via teleconference)
Dr. Stephen A. Williams (Present for closed session via teleconference)

Ex officio members present:
Dr. James G. Smirniotopoulus
Dr. Vincent L. Vilker
Dr. Andrew Watkins

Ex officio members absent:
Dr. Bruce H. Hamilton
Dr. Michael Leavitt
Dr. Elias A. Zerhouni

[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.

Executive Secretary:
Dr. Anthony Demsey

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

Dr. Prabha Atreya
Dr. Richard Baird
Ms. Cherise Banks
Ms. Sheila Barrett
Ms. Angela Burks
Dr. Zohara Cohen
Ms. Nancy Curling
Ms. Shirley Finney
Ms. Pamela Galpin
Dr. David George
Ms. Colleen Guay-Broder
Dr. John Haller
Dr. Donald Harrington
Dr. William Heetderks
Ms. Christine Hollingsworth
Ms. Elaine Jagode
Ms. Jeanellen Kallevang
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Henry Khachaturian
Dr. Brenda Korte
Dr. Albert Lee
Ms. Danielle Lewis
Dr. Hector Lopez
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Nicholas Mitrano
Mr. Joe Mosimann
Dr. Peter Moy
Dr. Robert Nerem
Mr. Aaron Nicholas
Ms. Donna Pearman
Dr. Grace Peng
Dr. Roderic I. Pettigrew
Dr. Belinda P. Seto
Ms. Karen Sheilds
Ms. Theresa Smith
Ms. Chantell Stevenson
Ms. Casey Stewart
Ms. Shana Townsend
Ms. Florence Turska
Ms. Stacy Wallick
Dr. Fei Wang
Ms. Latoya Wilhite
Ms. Li-Yin Xi
Dr. Yantian Zhang

Members of the public present for portions of the meeting:
Mr. Mark Brown, MasiMax Resources
Ms. Barbara Dunlavey, Biomedical Engineering Society
Ms. Lynne Fairobent, American Association of Physicists in Medicine
Ms. Pat Ford-Roegner, American Institute for Medical and Biological Engineering
Dr. Gary Glover, Stanford University
Ms. Mariana González del Riego, Rose Li and Associates, Inc.
Ms. Jeanie Kennedy, American Academy of Orthopedic Surgeons
Mr. Ed Nagy, Academy of Radiology Research
Mr. Chris Peterson, SRI International
Dr. William Sansalone, Georgetown University
Ms. Jennifer Solomon, Rose Li and Associates, Inc.
Dr. David R. Walt, Tufts University

Other Federal employees present:
Dr. David Brown, Food and Drug Administration
Dr. Mrunal Chapekar, National Institute of Standards and Technology
Ms. Carol Fitzpatrick, National Center for Complementary and Alternative Medicine
Dr. Albert Lee, National Institute of Standards and Technology
Dr. Kyle Myers, Food and Drug Administration
Dr. Ross Shonat, Center for Scientific Review

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey called the 10th NACBIB meeting to order. 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 acknowledged former Council member Dr. C. Douglas Maynard, who received the Gold Medal Award from the Radiological Society of North America in recognition of his exemplary service to the science of radiology. Dr. Maynard played an instrumental role in the creation of the NIBIB and served on the Advisory Council for 4 years.

Dr. Pettigrew also introduced three new staff members.

- Dr. Hector Lopez is Program Director in the Division of Applied Science and Technology. Before coming to the NIBIB, he worked for the Food and Drug Administration, Center for Devices and Radiological Health and at the National Institutes of Health (NIH) Center for Scientific Review. His research interests include ultrasound imaging, imaging system performance, perception, signal detection and processing, and image processing.
- Dr. Richard Baird is Director of the Division of Interdisciplinary Training at the NIBIB. His many achievements include founding and directing the Inner Ear consortium and serving as Director of Research for the Harold W. Siebens Hearing Research Center at the Central Institute for the Deaf. His research interests include transduction and information processing in hair cells; hair cell development, repair, and regeneration; and synaptogenesis and injury-induced synaptic remodeling.
- Mr. Joe Mosimann is Budget Analyst in the Budget Division. He has many years of experience in the NIH Office of the Director.

III. Director's Report: Dr. Roderic Pettigrew

Dr. Pettigrew summarized activities of the Institute since the September 2005 Council meeting, including the budget outlook, significant events, and scientific highlights and initiatives.

NIBIB Budget
The NIBIB fiscal year (FY) 2006 budget is approximately $297 million (0.5 percent less than FY 2005). The FY 2006 appropriation reflects an across-the-board one-percent rescission

imposed by Congress on the NIH to increase national funding for Gulf Coast reconstruction and overseas military operations.

Funds for FY 2006 generally have been distributed similarly to FY 2005 funds. The greatest change from last year is an 82-percent increase in intramural funding. Other areas, such as training mechanisms and contracts, reflect percentage changes but do not vary substantially in actual dollar amounts. Research project grants (RPGs) constituted the only budget category in which funding decreased from the previous year. Dr. Pettigrew indicated that the impact from this reduction would not be significant given the large number of funds allocated to RPGs. NIBIB funding for the NIH Roadmap initiative increased approximately 41 percent to $2.7 million for FY 2006; this amount is less than originally allocated, as the Roadmap initiative also was subject to the trans-NIH percentage cuts.

Planned FY 2007 initiatives include a request for applications (RFA) on image-guided interventions (IGIs), an RFA on point-of-care technologies, and a program announcement on regenerative medicine.

Quantum Projects
Dr. Pettigrew updated Council members on the status of the Quantum Projects Exploratory Grants, for which an RFA was released on November 18, 2005. The initiative will support collaborative research and feasibility studies that require innovative technological approaches to address major targeted health problems, resulting in profound (quantum) improvements in health care. Under the P20 mechanism, Phase I will provide $400,000 to $700,000 per year for 3 years. Applications are due February 21, 2006; letters of intent were due in January, and the response to the RFA has been considerable. The NIBIB has released a fact sheet about the program, and a pre-application Web/teleconference was held December 12, 2005, to review the concept of the initiative and answer questions from potential participants. In addition, a Quantum Grants Committee, comprised of NIBIB program and review staff, has been established.

Howard Hughes Medical Institute (HHMI)/NIBIB Interfaces Initiative
The NIBIB has partnered with HHMI to support interdisciplinary graduate education in biomedical research institutions. In Phase I, HHMI will award $10 million in grants to 10 institutions to support the establishment of training programs in emerging interdisciplinary fields for 3 years. Phase II will be funded by the NIBIB to sustain these programs through the following 5 years.

Regional Grantsmanship Seminars
The Grantsmanship Seminars are intended to provide an overview of NIBIB funding opportunities as well as NIH application, review, and grant-making processes and policies. A seminar was held October 17, 2005, at the George Washington University Marvin Center in Washington, DC. The spring 2006 seminar is scheduled for April 18, 2006, at the North Carolina Biotechnology Center in Research Triangle Park, NC, and the fall 2006 seminar will be held in Houston, TX. Additional information on hosting a seminar can be viewed at http://www.nibib.nih.gov/nibib/File/Funding/NIBIB_Grantsmanship_host_logistics.pdf.

NIBIB Web Site Launched
The redesigned NIBIB Web site was launched in October 2005 and can be found at http://www.nibib.nih.gov. The new design is intended to be informative for researchers and grantees, stakeholders, and the lay community.

NIBIB Fifth Anniversary Celebration
A celebration is being planned in recognition of the NIBIB's fifth anniversary. Details will be made available as plans for the celebration progress.

IGI Federal Interagency Retreat
Representatives from the NIBIB and other NIH Institutes and Centers (ICs) joined participants from the Food and Drug Administration, the National Aeronautics and Space Administration, the National Science Foundation, the Department of Defense, the Department of Energy, and the National Institute of Standards and Technology for a Federal interagency retreat on January 24, 2006. The goal was to identify the highest-priority grant challenges that can serve as short-term (1 to 5 years) and long-term (5 to 10 years) goals to advance IGI.

Electronic Submission of Applications
The NIH is expecting to complete the transition toward electronic submission of all competing research grant applications by September 2007. Additional information and updates are available at http://era.nih.gov/ElectronicReceipt/.

Office of Portfolio Analysis and Strategic Initiatives (OPASI)
Established within the NIH Office of the Director, OPASI will support regular, trans-NIH scientific planning and initiatives, and an adaptive priority-setting process for identifying areas of scientific and health-improvement opportunities. The mission of OPASI is to provide NIH ICs with the methods and information necessary to improve the management of their large and complex scientific portfolios; to identify— along with multiple other inputs—important areas of emerging scientific opportunities or rising public health challenges; to assist in the acceleration of investments in these areas, focusing on those involving multiple ICs; and to coordinate and make more effective use of the NIH-wide evaluation process. The new office also will identify compelling initiatives based on proposals from individual scientists, stakeholders, and organizations outside of the NIH.

OPASI will be comprised of three divisions under the OPASI Director: The Division of Resource Development and Analysis, the Division of Strategic Coordination, and the Division of Evaluation and Systematic Assessments. An OPASI Council will include representatives from each IC to provide oversight. Each IC will nominate three candidates from their individual councils, and the NIH Director will make the final selections and ensure a broad range of expertise. Recruitment for an OPASI Director is ongoing.

Scientific Initiatives and Highlights
Dr. Pettigrew highlighted the recent work of several NIBIB grantees.

- **Dr. Artur Olszak**, DMetrix, Inc., has produced an array-microscope slide scanner system that eliminates the need to package and mail pathology slides for tissue analysis. The

technology involves scanning a pathology slide and creating a digital image with preserved resolution that is achieved using an array of miniature microscopes. This allows the scanning of the slide at 10 times the speed of a conventional microscope. Once digitized, the images can be sent as electronic files.

- **Dr. David Kleinfeld**, University of California, San Diego, has been using two-photon laser-scanning microscopy to investigate the relationship between the arterial architecture on the surface of the brain and the preservation of blood flow in the cerebral cortex. This imaging of cortical surface microvessels has revealed a robust redistribution in blood flow after vascular occlusion: A distal vessel reverses the course of the blood to supply another vessel and thereby preserves flow.
- In an intramural collaboration between the NIBIB, the National Institute on Drug Abuse, and the National Institute of Diabetes and Digestive and Kidney Diseases, researchers have developed a positron emission tomography radiotracer to study corticotrophin-releasing factor receptor binding in the prefrontal cortex of the rhesus monkey using *in vitro* autoradiography. The tracer saturates the receptors, and its low, nonspecific binding enables it to reach the intended target directly. This could have an application in studying mental health, as corticotrophin-releasing factor is a neurotransmitter believed to play an important role in insomnia and depression.
- **Dr. Chien Ho**, Carnegie Mellon University, has developed a magnetic resonance imaging technique that allows the tracking of organ transplantation rejection and the monitoring of the movement and behavior of immune cells. Currently, the only method for tracking organ rejection is biopsy, a frequent, invasive process with problems that include sampling error. Dr. Ho and coworkers labeled macrophages *in situ* by injecting iron-oxide particles into rats after heart transplantation. This allows for the tracking of machrophage infiltration, which in turn, permits researchers to observe the process of organ rejection in detail.
- **Dr. David Kaplan**, Tufts University, and **Dr. Gordana Vunjak-Novakovic**, Massachusetts Institute of Technology/Columbia University, have been working on engineering a cardiac patch that is capable of synchronized cardiac activity. The approach involves packing human stem cells in a density consistent with that of myofibrils and exposing them to an alternating electrical stimulus similar to what the cells would experience in the native cardiac environment. When the cells within the myocardial construct are stimulated with electrical activity, they mimic cardiac cells, demonstrating synchronized contractile activity.
- **Dr. Stephen Badylak**, University of Pittsburgh, has been very successful using the matrix-based approach to tissue engineering. A section of tissue is placed in the native bed where it recruits the existing progenerative cells and stimulates the regeneration of native tissue. In this particular study, the tip of a man's index finger had been sliced off. Although the intention was to achieve a complete closure of only the fingertip wound, the entire tip of the finger regenerated, and the finger regained full functionality.

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

Council Regulations, Policies, and Procedures

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

Future NACBIB Meeting Dates
The next NACBIB meeting is scheduled for May 19, 2006, at the Marriott Bethesda North Conference Center. Dr. Demsey acknowledged that the May 2006 NACBIB meeting will be longer than the January 2006 meeting. Dr. Demsey also noted a change in the first of the two Council mailings, which is sent 2 months in advance of every NACBIB meeting; the first mailing will no longer be mailed as a hard copy but will be sent electronically to all members with a copy to their administrative assistants. The September 2006 meeting will be held at the Residence Inn in Bethesda, MD.

Approval of September 14, 2005, NACBIB Meeting Minutes
A motion was entertained to approve the minutes of the September 14, 2005, NACBIB meeting. The minutes were approved unanimously without modification.

V. Annual Report on Animal and Human Subjects Concerns: Dr. Anthony Demsey

Dr. Demsey reported on the involvement of humans and animals in research supported by the NIBIB for FY 2005 in response to a request by Council for an annual update on these topics. Approximately 33 percent of applications received by the NIBIB in FY 2005 proposed research using animals, compared to about 37 percent for all NIH applications. Approximately 10 percent of incoming NIBIB applications (compared to 5 percent of all incoming NIH applications) had animal welfare concerns. Following the resolution of concerns and approval by the Office of Laboratory Animal Welfare, about 15 percent of these NIBIB applications (10 percent of the NIH applications) were funded. The NIH and the NIBIB consider animal welfare to be critical to the conduct of research; therefore, no award is made until a concern is resolved.

In contrast, the NIBIB received a much smaller proportion of research applications involving the use of human subjects (20 percent) compared with the NIH as a whole (40 percent). Human subject applications with concerns also were proportionately fewer than those for the entire NIH (approximately 10 percent for the NIBIB versus 14 percent for all of NIH), and the number of applications with resolved concerns that were awarded was relatively small. As with the use of animals in research, the NIH and the NIBIB consider the involvement of humans in a research endeavor to be critical, and all means must be used to protect the health and safety of these individuals. Therefore, no award is made until a concern is resolved.

VI. Research Portfolio and Strategic Implementation Update: Dr. William Heetderks

Portfolio Review
Prior to providing an update on the NIBIB grant portfolio and strategic implementation plan, Dr. Heetderks reminded Council members that the primary goal of the implementation plan is to have a successful investigator-initiated extramural research program focused on the discovery, development, and application of science and technology to improve health.

A comparison of the numbers of R01/R21 grants funded between FY 2003 and FY 2005 across different research areas revealed that between 20 and 40 grants have been awarded in many of the research areas. A significant decrease in the number of awards occurred in magnetic resonance imaging research, which was offset by an increase in image processing research. The areas of surgical technologies, modeling and simulation, image processing, and biomechanics increased in the number of grants by 100 percent or more between FY 2003 and FY 2005. Tissue engineering, modeling and simulation, biomechanics, and advanced biomaterials had the greatest increase in new competing awards in FY 2005, whereas the areas of nuclear medicine, medical devices, bioelectric/biomagnetic, and biosensors saw significantly fewer new awards.

Dr. Heetderks then presented a table illustrating developments in the NIBIB grant portfolio from FY 2002 through FY 2005, divided into three categories: (1) NIBIB competing awards, (2) NIBIB noncompeting awards, and (3) awards that were transferred from other Institutes. FY 2003 showed the greatest increase in the number of competing awards. He explained that the percentage of non-transferred awards (i.e., awards submitted to and awarded by NIBIB) has continued to increase over the past 4 years.

Implementation Activities
In reviewing past, current and upcoming implementation activities within NIBIB program areas, Dr. Heetderks emphasized that the implementation process is dynamic, and as a result, a careful record of ideas, planned activities, and completed activities is being kept across divisions. As an example, he briefly highlighted a number of focus areas within the Division of Applied Science and Technology. Other initiative areas are being pursued by the Division of Discovery Science and Technology and the Division of Interdisciplinary Training.

***In vivo* Optical Imaging**: Two *in vivo* optical imaging activities will be taking place this year: (1) the *Fifth Inter-Institute Workshop on Optical Diagnostic Imaging from Bench to Bedside* at the NIH will be held in October 2006 and (2) the 2006 *Institute of Electrical and Electronics Engineers International Symposium on Biomedical Imaging: From Nano to Macro* will be held in April 2006. Future ideas include a workshop to evaluate the current status of optical imaging technologies and clinical applications to formulate strategies to accelerate optical imaging translation and an optical imaging initiative in 2007.

Image-Guided Interventions: IGI workshops were held in 2002 and 2004. On January 24, 2006, an inter-agency IGI special interest group organized the IGI Federal Inter-Agency Retreat. Participants representing various Federal agencies and NIH ICs sought to identify (1) the highest-priority Grand Challenges that can serve as short- and long-term goals to advance IGI, (2) the resources and courses of action across the Federal agencies needed to implement the

Grand Challenges for IGI, and (3) the metrics of success for the Grand Challenges. An IGI RFA is planned for release in 2007.

Clinical Microimaging Technologies: This initiative area, which is being pursued in collaboration with other Institutes, supports the research and development of high-resolution microscale and micromodality imaging technologies for *in vivo* use in clinical applications. An RFA entitled "Toward Imaging the Pancreatic Beta Cell in People" was released in December 2005, and awards will be made in September 2006.

Following Dr. Heetderk's presentation, a Council member inquired about the RPG category, which experienced the greatest decrease in budget and number of grants in FY 2005, and how it will be affected in FY 2006. Dr. Pettigrew replied that it is difficult to reduce funds without making significant cuts to the largest award mechanism category, RPGs. However, he anticipated that the NIBIB payline will not be significantly lower than that of the NIH as a whole. In response to a follow-up question, Dr. Heetderks explained that the projected payline is 13 percent, with a continuing 5-percentage point increment for new investigators. Dr. Pettigrew expressed optimism that the year would end with a slightly higher payline than currently projected.

One Council member pointed out that the NIBIB budget cuts seemed to go against Congress's original intention. Dr. Pettigrew explained that although Congress indeed recognized the need for the formation of the NIBIB and requested a plan from the NIH to help the Institute realize its potential, the economic environment is now very different. Operating rules have changed, and other areas have taken precedence (e.g., funding for recent natural disasters).

Another Council member recalled that periods of tight funding had been anticipated and that precautionary steps were taken to establish priority areas. However, the current financial situation is more dire than expected. Consequently, staff and Council members were encouraged to review the strategic plan before the May 2006 meeting and to determine which areas should be given greater priority when spending the limited funds that Congress has appropriated.
Dr. Belinda Seto noted that the NIBIB funding plan is available on the Web site, and the plans for every Institute soon will be available on a single site. Dr. Pettigrew added that the NIBIB pay plan is comparable to those of other Institutes.

VII. NIBIB Training and Career Development: Dr. Richard Baird

During its startup, the NIBIB expanded the number and funding levels of many training and career development programs. Now, the NIBIB faces the challenge of (1) reassessing training needs and programs, (2) reducing the growth of training funding levels, and (3) anticipating the entry of HHMI-NIBIB programs to the training portfolio as it transitions from rapid to slower growth.

Needs Assessment
In FY 2005 to FY 2006, the NIBIB and ORCMacro began an ongoing study to determine the origins and characteristics of NIBIB trainees. In this study, key academic, industry, and government leaders have been interviewed, and training data from the NIH, NSF, HHMI, and

Whitaker Foundation are being analyzed statistically to identify broad trends. This study will allow the NIBIB to determine the number of researchers in biomedical imaging and bioengineering, including the number originally trained in other disciplines and the number from underrepresented populations. It will also allow the NIBIB to assess the distribution of these researchers across employment sectors, their sources of support, and their paths to success. In FY 2007, the NIBIB intends to follow up this study with a post-assessment workshop attended by assessment interviewees and Council members. The NIBIB is also preparing an internal database of predoctoral, postdoctoral, and early-career investigators supported by training and non-training grants.

HHMI-NIBIB Graduate Training Program
The first phase of the HHMI-NIBIB Graduate Training Program entails 3 years of HHMI funding to establish interdisciplinary training programs at institutions selected through a peer-review process. The second phase consists of 5-year peer-reviewed NIBIB T32 training grants to sustain the programs during their critical early years. This latter phase will present a significant challenge to the NIBIB, potentially shifting the program balance of the current portfolio.

Training Budget
The NIBIB experienced a rapid growth in T, F, and K awards from FY 2002 to FY 2004, with steady growth continuing over the past two years. However, it will be difficult to sustain this progress in the current budget climate.

Challenges to Institutional Training Awards
In response to this challenge, Dr. Baird proposed to make the following changes to T32 Institutional training awards:
- Fund new T32 Institutional Training Grants based on quality and program balance.
- Encourage a mix of smaller/specialized and larger/broad-based training grants to fit the needs of the extramural community better.
- Slow the growth of training slots on the largest training programs.
- Implement a proposed new trans-NIH tuition guideline by (1) capping the tuition formula, (2) eliminating the tuition formula, or (3) keeping the tuition formula but reducing the number of T32 Institutional training awards.

Changes to Fellowship Awards and Career Development Awards
There has been a substantial increase in the number of F31 predoctoral applications as awareness of this program has grown in the extramural community and other NIH Institutes with interests in biomedical imaging or bioengineering have eliminated their participation in this program. Such growth is not sustainable; therefore, the following changes have been proposed:
- Redirect F31 Kirschstein Individual Predoctoral Awards (exclusive of F31 Minority and Disability Awards) to a small number of outstanding investigators in NIBIB mission areas.
- Redirect F32 Kirschstein Individual Postdoctoral Awards to investigators with quantitative backgrounds.
- Redirect F33 Individual Senior Fellowship Awards to applicants with extensive mentoring experience for the primary purpose of training younger investigators.

In addition, K awards will be redirected to early-career investigators, especially those with quantitative backgrounds, and mid-career investigators with extensive mentoring experience.

Training Priorities
Dr. Baird explained how all of the above changes would affect the priorities of the training division. In feeding the pipeline for undergraduate and graduate students, the NIBIB-NSF Bioengineering and Bioinformatics Summer Institutes (BBSI) Program will be expanded to a larger number of Institutes, and the NIH Biomedical Engineering Summer Internship Program (BESIP) will continue to bring more students into the field of biomedical research. The NIBIB also will continue targeting underrepresented populations by maintaining the F31 and R01 diversity supplements, recruiting additional points-of-contact for minority programs, and increasing outreach and recruitment efforts.

Because the average age at which investigators receive their first independent funding has escalated considerably over the past 20 years, a new mechanism, the Pathway to Independence Program, is being implemented. The NIH will fund approximately 175 awards, of which the NIBIB will fund five. The awards are for 5 years of total support, consisting of two phases: The first phase will provide up to 2 years of mentored postdoctoral support, and the second phase will fund 3 years of independent research support contingent on administrative review and securing of a tenure-track position. The applications will be reviewed either in-house or by clustered IC review. Dr. Baird asked Council members to consider the appropriateness of this approach in response to the career transition problem. Specifically, he asked about its appropriateness for all of the cohorts supported by the Institute and whether other mechanisms designed to help early-career investigators should be entertained in addition to this program. He also requested feedback on how this program should grow from the NIBIB's initial level of commitment.

The NIBIB is continuing many of its past efforts for developing clinical researchers, including dedicated T32 training slots for medical students, the residency supplement program for both clinical residents and clinical fellows, the loan repayment program for clinical residents, and the mentored (K08) and mid-career (K23) patient-oriented research programs for clinical fellows. The residency supplement program is currently in the middle of its third round. It has been a very successful program, based on previous Council recommendations, and will be considered for re-announcement again in summer 2006.

For training at the interface between the physical and biological sciences, a mission of the NIBIB is to attract quantitative scientists to biomedicine. The BBSI and BESIP training programs will bring in undergraduate and graduate students, the HHMI-NIBIB partnership will offer new interdisciplinary graduate programs and bring more investigators to the field, and the K25 Career Development Program will support investigators from the physical sciences who want to transition to biomedical research. Interfacing clinical and basic researchers is part of this priority, and Dr. Baird suggested developing future initiatives to promote the co-mentoring and cross-training of these two cohorts.

Discussion
One Council member asked about the NIBIB's objectives—what assessments were being done in regard to demand, and why, considering the limited funds, the NIBIB is recruiting more trainees.

Dr. Baird emphasized that the Institute is taking conservative steps and talking to representatives from the employment sectors in an effort to clarify entry and exit points for trainees. He suggested broadening the definition of success to include the research and development of new technologies, whether achieved in the academic or other employment sectors. Having access to data from other training foundations, as well as the NIH, will be beneficial because the statistical sample within the NIBIB is quite small. The small size of this sample is advantageous for now, allowing the creation of a data base with all of the awardees since inception; however, more data are still needed from the extramural community. Dr. Baird encouraged taking small, prudent steps now and taking more aggressive steps in the future in light of further information.

In response to a question about the timing of the workshop and the evaluation data, Dr. Baird explained that the ORCMacro assessment study is expected to be completed by April 2006. He will work with other NIBIB representatives to review the data before setting up the post-assessment workshop. The NIBIB also will expand its effort to the NIH more broadly, and will request assistance from the NIH Office of Evaluation to carry out a full-scale evaluation of its training and career development programs. It is helpful to see how these mechanisms have been used by other NIH ICs and their appropriateness for NIBIB efforts. Approximately 4 to 5 percent of the NIBIB budget is devoted to training or training-related programs, just slightly over the average for all NIH ICs.

A Council member expressed concern that the pressures put on the Institute by current paylines could be interpreted as a need to reduce the number of trainees. Since both the research community and industry continue to see strong demand for new trainees, it would be imprudent to reduce the number of trainees simply because the NIH payline has fluctuated in recent years. The participant added that the Pathway to Independence initiative is an excellent program that fits a very important need. However, there was some concern over a proposed restriction of the award to those progressing to tenure-track positions only. An increasing number of permanent appointments are being made in institutions at the research level, that is, research assistant professorships and research associate professors that are not tenure-track, but that are dedicated almost entirely to research. In that member's opinion, investigators under the Pathway to Independence initiative should not be excluded if they are not on a tenure track.

Dr. Baird explained that the main concern of the NIH is that these investigators are treated fairly and that the value of the award is recognized by extramural institutions. The key is independence; the NIH will look at whether there is a true institutional commitment to the candidate who is the recipient of one of these awards. The intent is not to exclude individuals but rather to bring them successfully into their first independent funding and, hopefully, on to future grants. Dr. Baird assured the Council that the precise language had not yet been decided upon. The Council member suggested that the NIBIB ask applicants for a statement from the institution describing the position, rather than just providing the position title. Dr. Baird agreed, and explained that the NIH is looking for evidence of an independent position, i.e., one in which a start-up package or some institutional commitment is made, and that there will probably be some flexibility within the broad guidelines.

Another Council member commented that it would be important to obtain the perspective of both the bioengineering and the imaging communities from the academic, clinical, and industrial

perspectives to answer the important questions that have been posed. The National Academy of Engineering (NAE) has run a successful series of meetings called *Frontiers in Engineering* that have an interdisciplinary focus and bring together both the academic and industrial communities. The NIBIB may be able to take the lead in a similar series of meetings, perhaps with NAE and IOM support, to discuss questions at the interface between these communities.

On the topic of future initiatives to promote the co-mentoring and cross-training of clinical and basic researchers, one attendee suggested including the technology aspect in both the mentoring and training processes. Dr. Baird acknowledged this possibility and described his interest in establishing internships in industry and finding ways to interact better or partner with key companies. Dr. Baird agreed to follow up with appropriate contacts to see how this could be implemented.

Another attendee asked how institutions are informed about these programs so that potential candidates, including medical students and residents, can learn about these opportunities. Dr. Baird agreed that it would be helpful to identify an office within each institution that is responsible for keeping students and residents informed. He suggested assigning program staff to interface with specific organizations and institutions.

Dr. Baird was asked to elaborate on the HHMI partnership and the subsequent change in focus of training grants. He indicated that this program will certainly bring additional mathematical rigor to the NIBIB training programs, including computational modeling and imaging informatics, but it is not yet clear how these programs will evolve over the next 3 years. He also expressed the need for the training portfolio to mirror the research portfolio more broadly. This also gives the NIBIB an opportunity, for relatively small amounts of money, to anticipate new growth areas in biomedical imaging and bioengineering. He indicated that it was certainly possible that significant changes in the training portfolio might occur depending on how the HHMI programs evolved and how competitive they were with existing programs.

VIII. Scientific Presentation—Sensors and Microsystems Research: Dr. Brenda Korte

Dr. Korte provided an overview of the Sensors and Microsystems program area, part of the ongoing series of program talks to communicate the scientific coverage of the Institute. This area covers the development of sensor technologies for the detection and quantitation of clinically relevant analytes in complex matrices and the miniaturization of analytic processes to realize significant improvements in performance over macroscale devices on the microscale. From an applications perspective, the main emphasis is on *in vitro* identification and quantitation of analytes in biological fluids, as well as aspects of noninvasive monitoring.

The number of NIH awards in biomicroelectricomechanical systems (BioMEMS) and microfluidics (the study of fluids at the microscale involving the development of pumps, mixers, reservoirs, and valves) has continued to climb steadily over the past 6 years, with nearly 200 active grants in FY 2005 compared with slightly more than 50 active grants in FY 2000. These grants focus on the development of enabling technologies central to the major trends in biomedical sciences and the future of health care. BioMEMS and microfluidics technologies provide the necessary platforms for high-throughput analysis of complex biological systems, and

these studies, in turn, are improving our understanding of the molecular bases of disease and enabling earlier disease detection, with the ultimate goal of disease prevention. There is also a need to focus on containing health care costs and providing low-cost alternatives to laboratory-based measurements. These devices provide that capability by moving specific analyses to the point of care.

Recently, each program director evaluated his or her portfolio of active grants as part of the effort by the NIBIB to develop an implementation plan and a follow-up to the strategic planning process. The results of the analyses for this particular program are as follows.

As of April 2005, there were 79 active NIBIB grants in the sensors and microsystems area. Approximately half of these were focused on the development of enabling technologies (i.e., the development of novel detection methodologies). Eighteen grants focused on clinical laboratory diagnostics or *in vitro* diagnostics. The NIBIB has a small portfolio in noninvasive monitoring (seven grants) and in biodefense (eight grants, primarily transfers from the National Institute of Allergy and Infectious Disease). In the area of drug discovery and high-throughput screening, the NIBIB had three active grants; however, there has been growth in this area since April 2005 through NIH Roadmap efforts. There were four active grants in the area of basic biology, primarily the result of National Institute of General Medical Sciences coverage in this area.

The program was developed in part through two key initiatives, the first of which focused broadly on sensor development and validation, and the second targeted at the development of sensors *in vivo*. Several workshops and conferences have been held in recent years to identify challenges and opportunities in the sensor area, including the 2002 Bioengineering Consortium Symposium, focused on sensors in biological research in medicine. In addition, the NIBIB cosponsored an international assessment of biosensing research and technology, coordinated through the World Technology Evaluation Center in Baltimore, MD. The sensor and microsystem area also has been represented within NIH Roadmap activities, particularly through an RFA focused on the development of high-throughput screening instrumentation for which the NIBIB served as co-program lead with the National Human Genome Research Institute.

Future directions in the sensor and microsystem area focus on the development of integrated sensor and lab-on-a-chip devices for point-of-care testing (POCT). Recent emphasis within this technology area has been on the development of components such as novel detection approaches, with limited testing on complex samples. The ultimate goal is to realize the practical applications of the advances that have occurred over the past decade and to have these devices used by practicing clinicians. As a result, user interface and robustness are important parameters.

From the clinical perspective, there are significant motivations for increased use of POCT. Many of these relate to changes in the health care delivery system, including the shift toward a patient-centered approach; greater emphasis on primary care and home health care; increased use of the Internet, both by providers and patients; and an ongoing focus on reducing health care costs. Improving health care accessibility requires user-friendly technologies to enable complex, laboratory-based testing in an outpatient setting, low-cost solutions, and informatics. Finally,

one of the main drivers for the area has been the emphasis on improving outcomes through rapid analysis.

NIBIB/National Heart, Lung, and Blood Institute (NHLBI)/NSF Workshop
Although there is generally a broad acceptance of the potential of POCT in the clinical environment, it is often difficult to make the business case for applying a specific clinical analysis to the point of care. Thus, it is especially critical to involve the clinical community early in the process of technology development. Dr. Heetderks reported that the NIBIB is organizing a workshop (co-sponsored by the NHLBI and the NSF) to help the community better understand the challenges and opportunities in the area of point-of-care technologies. The workshop will address the relevant science and core technology areas for POCT: Sensors and microsystems, lost-cost imaging, noninvasive monitoring, and telehealth/informatics. It will also focus on the clinical needs and opportunities in rural health care settings with potential for the greatest impact on health care accessibility: primary care, emergency medical services, home- and community-based care, and developing countries. The meeting is planned for April 11 and 12, 2006, and currently is open for registration.

Research Highlights
Dr. Korte concluded her presentation with research highlights that focus on cell analysis as a theme of significant interest.

- **Dr. Mehmet Toner**, Massachusetts General Hospital, is Principal Investigator of a BioMEMS Resource Center (P41) grant to provide unique capabilities to biomedical investigators to probe, perturb, engineer, and analyze biological cells and tissues through the use of microsystems technologies. This relatively new center has two core research and development projects: (1) the development of microfluidic systems to manipulate and sort cells without altering phenotype; and (2) the development of microfabrication tools for tissue engineering applications.
- **Dr. Nancy Allbritton**, University of California, Irvine, is developing an automated microsystem platform for the analysis of kinase assays on patient cells. The goal is to design a system to measure the cell-to-cell heterogeneity in response to varying exposure to therapeutic agents. Currently, the system consists of an integrated mesoincubator used to load reporter molecules into the cells, a microfluidic system for single-cell isolation, an optical system for cell lysis, an electrophoretic separation component, and a fluorescence detection component.
- **Dr. Joel Voldman**, Massachusetts Institute of Technology, is developing a novel approach to separate cells for cell-based screening, based on changes in electrical properties that occur when cells accumulate varying numbers of biomolecules (i.e., “isodielectric separation”) The utility of this approach could impact upon several areas, including the production of protein therapeutics in *Escherichia coli* and the production of microbial or medically important polymers using microbial techniques. Both of these processes can be optimized by screening for strains that demonstrate enhanced production of biomolecules.
- **Dr. Carl Hansen**, University of British Columbia, is developing a single-cell chemical genetics platform, a microsystem capable of performing highly parallel quantitative analysis on cells exposed to a time-varying chemical environment. When completed, the microsystem will consist of 64 perfusion chambers, addressable in groups of 8. The advantage of this

approach is the fluidic design, which allows for scale-up in the number of channels, with only limited additional complexity in the fluidic control portion.

Dr. Korte then introduced guest speaker Dr. David Walt, Robinson Professor of Chemistry at Tufts University. Dr. Walt is the Scientific Founder and a Director of Illumina, Inc., and is a fellow of the American Association for the Advancement of Science. His research interests are in the field of sensors, with particular focus in the area of fiber-optic chemical sensors.

IX. Scientific Presentation—Sensors, Arrays, and Systems: Dr. David Walt

Dr. Walt elaborated on Dr. Korte's presentation, focusing primarily on sensors, arrays, and integration into systems.

Sensors
A sensor combines three distinct analysis steps that normally would have to be conducted in a laboratory: (1) obtaining a sample; (2) pretreatment, converting the sample into a solution that can be introduced into the analytical instrument; and (3) measurement. A chemical sensor transforms chemical information, ranging from the concentration of a specific sample component to total compositional analysis, into an analytically useful signal. Biosensors are chemical sensors that consist of three basic elements: a receptor (biocomponent), a transducer (physical component), and a separator (membrane or coating of some type).

Many sensors are based on one of the following transduction mechanisms: mass, thermal change, electrochemical change, or optical change. Different levels of information can be derived from various kinds of sensors. Determining the component requires a fairly sophisticated kind of system, and determining the amount of substance present requires an even more sophisticated device.

Dr. Walt presented a number of examples of current sensors for a variety of purposes. He discussed in particular one technology on the horizon—near-infrared glucose sensing. This measurement concept transmits harmless near-infrared light through a vascular region of the body and extracts glucose concentration from an analysis of the resulting spectrum. The results demonstrate the ability to distinguish glucose from lactate, urea, alanine, triacetin, and ascorbate in spite of overlapping spectra. This could have significant implications for diabetes management and related medical applications. In the near future, sensors will become smaller and less or non-invasive.

Arrays
Gene arrays (also called gene chip or oligonucleotide arrays) have three distinct areas of application:

- Genotyping, understanding population and individual differences, with the ultimate goal of understanding and genotyping individuals for susceptibility to a disease or ability to respond to a particular drug.
- Gene expression, where differences in the amount of genes expressed in individuals can correlate with protein concentration. The variations between diseased and healthy tissue can

yield correlations about what genes are expressed and up- or down-regulated in these two patient populations.
- Diagnostics, which is still a future goal, where the presence of particular sequences correlates with infection by biological agents or viruses.

The basic principle is that a single strand of DNA is attached to a surface, and when the target is present, it binds through complementary base pairing, generating tens of thousands of signals simultaneously. In commercial applications, automated, integrated systems for genotyping and gene expression currently test more than one million genotypes per day, per instrument. As the arrays get smaller, it becomes possible to measure multiple components simultaneously, and the cost of materials decreases.

Cells provide very different information from that gained from standard binding. Binding involves a molecule, a ligand, and a receptor, and it indicates an affinity among them. It cannot identify biological effects (i.e., whether a molecule can permeate a cell membrane). However, cell-based screening enables the use of function as an assay in addition to binding. Single cells are also important because diseases often have a single locus occurring in one cell. Thus, it is necessary to look at populations of cells on a single-cell basis. Cells have tremendous variability, but that variability correlates with genetic noise (differences in how genes are expressed and transcribed) and possibly some aspects of gene regulation.

One current project on calcium oscillations with exposure to an agonist demonstrates the diversity in cell response; although all were challenged simultaneously with the same concentration of compound, there was significant innervation. Dr. Raoul Kopelman, University of Michigan, is studying more diagnostic applications in single-cell measurements. The idea is either to inject or interrogate a minimally invasive sensor. Dr. Kopelman's innovation is to attach everything to nanoprobes called PEBBLEs. These have a high amount of functionality and generate a fluorescent signal indicating that a nanoparticle is selective and sensitive to the variable being tested.

The problem with the typical kind of array formats is that 10,000 sensor readings are needed to measure 10,000 substances. This is an area of concern, as there are few very good receptors. It may be decades before it is possible to measure tens of thousands of molecules that may be the early indicators of disease. The alternative approach is to use "sloppy" sensors. The olfactory system is essentially a sloppy sensor, using numerous receptors that bind to a wide array of substances in a pattern.

Dr. Walt presented his work on holographic sensors, showing the response of sensors to a pulse of benzene, which is similar to a sniff. The pulse of benzene produces color changes that are collected on camera and digitized. These data are then used to train a smart, computation pattern-recognition system that can store numerous odors in its memory. The diagnostic application of this system is breath analysis. It is necessary to have many qualified control and diseased patients who contribute samples to account for heterogeneity in metabolism. For this technology to be translated into clinical use, it must be able to distinguish signal from background.

A newly funded project uses optical trapping to array particles or cells. The overall use of this method for cell manipulations is to capture thousands of beads or cells, perform an analysis on them, and selectively release or capture them. Dynamic arrays, rather than fixed arrays, enable the flow of cells or particles and quick analysis; they then allow release, capture, and another analysis, repeatedly.

Systems
Sensors and arrays all operate in the context of a system. Microfluidics applications include *in situ* measurements (process control and environmental monitoring), field analysis (environmental monitoring and forensics), medical diagnostics (point-of-care, emergency care, and closed-loop monitoring/dosing), and high-throughput laboratory analysis (combinatorial discovery, DNA sequencing, proteomics, drug metabolism, and pharmacokinetics).

Dr. Walt presented examples of lab-on-a-chip devices from Dr. Michael Ramsey's group at the University of North Carolina to show the ability to integrate substantial functionality. There are many applications of these devices, from diagnostics to laboratory analysis to measurement *in situ*. Because these devices are under computer control, they generally produce very high-quality data that can be presented similarly to a particular electropherogram, but on a small device. Flow cytometry, introducing individual cells onto a chip and interrogating a small volume, yields single-cell responses. The throughput can be on the order of hundreds of thousands per minute, as compared to tens of thousand per minute on a typical flow cytometer. Because individual patients can be analyzed using these devices, they have been commercialized by a number of companies.

Other Technologies
Dr. Walt discussed current nanotechnology, biotechnology, and bioengineering projects that are contributing to the production of new materials.

- **Dr. Rick Van Duyne**, Northwestern University, has developed nanoparticle array, localized surface, and plasmon resonance spectroscopy technology. He has created tiny gold-pattern arrays that interact with light and serve as transduction mechanisms, demonstrating new and high-functionality capabilities with great sensitivity.
- **Dr. Michael Sailor**, University of California, San Diego, is developing silicon photonic crystals of various colors and function.
- **Dr. Shuming Nie**, Emory University and Georgia Institute of Technology, used as a molecular label, zinc sulfide quantum dots that had been coated and prepared in slightly different sizes. Chemical and biochemical agents can be attached to these different particles via a binding agent. When injected into animals, these localize and emit different colors upon excitation. The different colors of quantum dots can be used in *in vivo* molecular imaging as imaging agents, for example, localizing at a tumor.
- **Dr. Chris Low**, University of Cambridge, has built holographic sensors that can be inserted into any substance (e.g., food) to indicate contamination.
- **Dr. Yoshio Umezawa**, University of Tokyo, has shown two proteins interacting, splicing, and reconstituting green fluorescent protein as a signal. Through molecular biology, signaling systems can be triggered when proteins interact.

Opportunities
Dr. Walt concluded his presentation by discussing the trend toward miniaturization and potential opportunities, and underscoring the necessity of system integration. In addition to lower basic material costs, in some cases, smaller instruments obtain more sensitive measurements and become more functionalized. Further, arrays can measure many parameters simultaneously, which is important to permit a holistic picture of system function. However, new materials are needed to realize the full potential of arrays and sensors. Dr. Walt noted that methods and technologies are being developed that can serve as research tools. These self-based diagnostic systems eventually may lead to diagnostics that will benefit patients. He stated that single-cell measurement capabilities are improving and that single-molecule sensitivity is possible. There is discussion within the NIH in general on doing exposure studies to determine whether single-site lesions can be detected in DNA or proteins.

Challenges include new sample types and collection; representative samples; sample preparation; diffusion/mass transport; biologically inspired, cell-based systems; sensitivity; data processing; power; deployment; and system integration.

Discussion
One Council member asked whether Dr. Walt and his team looked at intensity only or whether they found a discernible pattern in the sensors for the electronic/artificial nose study. Dr. Walt replied that some of the systems work only in testing, and these tend to be rather low in their ability to discriminate. He explained that they had pioneered the use of temporal data into what will be a biological system. His team has demonstrated conclusively tremendous improvement in discrimination ability by looking at temporal data, which are richer in information than equilibrium-based elements. Another Council member mentioned a recent paper on dogs smelling cancer with high accuracy and asked about the comparability of the electronic sensor. Dr. Walt emphasized the issue of sufficient receptor sensitivity to low levels of a substance in breath. Also, because dogs have brains, they process the exposures to cancer patients and control patients, and learn the difference.

One participant raised a concern over screening during a potential mass exposure as a result of bioterrorism. For example, if an anthrax exposure is confirmed in one or two people in a building, how will others in the building be checked for exposure? Dr. Walt explained that the issue is the time needed to test the samples. The best systems today can go from sample to result in approximately 30 minutes, and this will soon be possible on a large scale involving hundreds of thousands of patient samples.

X. Adjournment

The meeting was closed for review of applications at 12:30 p.m.

XI. Closed Session

This portion of the meeting, involving specific grant 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 and attachments are accurate and complete.[2]

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

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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 May 18 and 19, 2006, and corrections or notations will be stated in the minutes of that meeting.