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 26, 2007

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 13th meeting on January 26, 2007, at the Marriott Suites Bethesda in Bethesda, Maryland. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), presided.

In accordance with Public Law 92–463, the meeting was open to the public from 8:45 a.m. to 1:45 p.m. for the review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:45 p.m. to 3:15 p.m. for the discussion and consideration of individual grant applications.

Council members present:
Dr. Ronald L. Arenson
Ms. Rebecca M. Bergman
Dr. David J. Dzielak
Dr. Richard L. Ehman
Dr. Katherine W. Ferrara
Dr. Don Giddens
Dr. Augustus O. Grant
Dr. Rebecca R. Richards-Kortum
Dr. David Satcher
Dr. Stephen A. Williams
Dr. Frank C. Yin

Council members absent:
Dr. Robert I. Grossman

Ex officio members present:
Dr. P. Hunter Peckham, Veterans Administration
Dr. Anne Plant, National Institute of Standards and Technology
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences
Dr. Andrew Watkins, Centers for Disease Control and Prevention

Ex officio members absent:
Dr. Bruce H. Hamilton, National Science Foundation

[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.

Mr. Michael Leavitt, Department of Health and Human Services
Dr. Elias A. Zerhouni, National Institutes of Health

Executive Secretary:
Dr. Anthony Demsey

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

Dr. John Anderson
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. Angela Eldridge
Ms. Cheryl Fee
Ms. Shirley Finney
Ms. Carol Fitzpatrick
Ms. Pamela Galpin
Ms. Rajal Ganatra
Dr. David George
Ms. Pam Glikman
Ms. Colleen Guay-Broder
Dr. John Haller
Dr. John Hayes
Dr. William Heetderks
Dr. Lori Henderson
Dr. Rosemarie Hunziker
Ms. Jeanellen Kallevang
Dr. Chris Kelley
Dr. Dale Kiesewetter
Dr. Peter Kirchner
Dr. Brenda Korte
Dr. Lixin Lang
Dr. Richard Leapman
Dr. Albert Lee
Dr. Zheng Li
Mr. Bryan Linares
Dr. Hector Lopez
Dr. Xiao-Zhong (James) Luo
Dr. Ying Ma
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Nicholas Mitrano
Mr. Larry Morton
Mr. Joe Mosimann
Dr. Peter Moy
Mr. Aaron Nicholas
Ms. Donna Pearman
Ms. Allison Peck
Dr. Grace Peng
Dr. Karen Peterson
Dr. Roderic I. Pettigrew
Ms. Patty Runyon
Ms. Katie Serrano
Dr. Belinda P. Seto
Mr. Shaun Sims
Ms. Florence Turska
Ms. Stacy Wallick
Ms. Latoya Wilhite
Mr. Matt Wise
Ms. Li-Yin Xi
Dr. Yantian Zhang
Dr. Ruixa Zhou

Other Federal employees present:
Dr. David Brown, Food and Drug Administration
Ms. Chekesha Clingman, National Institutes of Health, Office of the Director
Mr. Francis Costello, National Institutes of Health, Office of the Director
Dr. Henry Eden, National Institutes of Health, Office of the Director
Dr. Valery Gordon, National Institutes of Health, Office of the Director
Dr. Diane Hannemann, National Institutes of Health, Office of the Director
Dr. Kyle Myers, Food and Drug Administration
Dr. Terry Phillips, National Institutes of Health, Office of the Director
Dr. Nancy Shinowara, National Institutes of Health, National Institute of Child Health and Human Development

Members of the public present for portions of the meeting:
Ms. Jennifer Ayers, American Institute for Medical and Biological Engineering
Dr. Kevin Cleary, Georgetown University
Ms. Renee Cruea, Academy of Radiology Research
Ms. Barbara Dunlavey, Biomedical Engineering Society
Dr. Dan Eckstein, NOVA Research Company
Ms. Mariana González del Riego, Rose Li and Associates, Inc.
Ms. Masuko Kaufman, Iri Sangyo Shimbun Press
Ms. Jeanie Kennedy, American Academy of Orthopaedic Surgeons
Ms. Christine Maisano, Rose Li and Associates, Inc.
Ms. Olivia Propst, NOVA Research Company
Ms. Susan Reiss, National Capitol Captioning

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey welcomed attendees and called to order the 13th NACBIB meeting. He reminded Council members that because the morning session of the meeting is 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

A. New Council Member

Dr. Pettigrew welcomed new *ex officio* Council member Dr. Anne Plant from the National Institute of Standards and Technology (NIST). Dr. Plant received her Ph.D. from Baylor College of Medicine, Houston, Texas, and is a research chemist and group leader of the Cell and Tissue Measurements Group in the Biochemical Science Division at the NIST. She is active in both basic and applied research including biophysical chemistry, interfacial science, and cell biology. Her current research interests include controlled surface chemistries at the microscale and nanoscale for studies of cell response to extracellular matrix proteins. She recently began a new program at the NIST to develop quantitative microscopy protocols for cell biology. At the NIST, Dr. Plant founded the Biomolecular Materials Group, which focuses on the formation and characterization of supported lipid membranes for application as sensors and for membrane

protein structure function studies. Dr. Plant previously served for 5 years as Editor of the American Chemical Society journal *Langmuir*.

B. Honors

- The Satcher Health Leadership Institute, named for Council member Dr. David Satcher, is being established at the Morehouse School of Medicine. The new Institute will receive support from the Robert Wood Johnson Foundation.
- NIBIB employees were honored at a recent meeting of National Institutes of Health (NIH) Institute and Center (IC) Directors for their contributions to the annual Combined Federal Campaign, a Government-wide fundraising drive to support various charities and philanthropic endeavors. As an Institute, the NIBIB exceeded its contribution goal by 200 percent, the largest percentage of the target goal achieved by any IC. Dr. Pettigrew commended NIBIB staff for their generosity.

III. Director's Report: Dr. Roderic Pettigrew

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

A. NIBIB Budget

At the previous Council meeting, Dr. Pettigrew announced that the NIBIB's fiscal year (FY) 2006 budget was approximately $296 million and that the President's proposed FY 2007 budget for the Institute is almost $2 million less than the FY 2006 budget. To date, the proposed FY 2007 budget has not been signed; through February 15, 2007, the NIBIB is operating under a continuing resolution at the level of the 2006 appropriation. If the resolution is extended beyond this date, the NIBIB will continue under the 2006 budget with a 0.5-percent increase to offset the 2006 rescission that reduced the NIH's actual funding level by 0.5 percent.

Dr. Pettigrew noted several key changes in the 2007 NIH Fiscal Policy for Grant Awards:

- No inflationary adjustments will be awarded for existing non-competing renewal applications in 2007. The savings that result from this new policy will be used to return the number of research program grant investigators to the level achieved in 2005, when that number was at an historic high.
- ICs will be able to supplement non-competing awards on a case-by-case basis.
- When making funding decisions close to the pay line, the primary goal of the Institutes will be to maintain the current number of new investigators. Thus, funding decisions close to the pay line will be prioritized as follows: New investigators, investigators renewing awards for the first time, and established investigators with applications in areas of great promise and high priority to the ICs.

B. NIBIB Significant Events

NIH Reform Act of 2006

The NIH Reform Act of 2006 was passed unanimously by Congress on December 8, 2006, and was signed by the President on January 15, 2007. Dr. Pettigrew described several of the bill's key provisions:

- Establishment of the Division of Program Coordination, Planning, and Strategic Initiatives (currently known as the Office of Portfolio Analysis and Strategic Initiatives, or OPASI) within the NIH Office of the Director.
- Creation of the Common Fund, which will serve as an incubator for trans-NIH projects until they mature and can transition to an IC. A Council of Councils (comprising members of various Institute Councils) will advise the NIH Director on how to prioritize these projects. While the Reform Act does not specify the amount in the Common Fund, the Act states that (1) the amount reserved for the Fund by the NIH Director cannot decrease (in percentage) from one fiscal year to the next, and (2) when the Fund reaches 5 percent of the NIH budget, the NIH Director, in consultation with the Council of Councils, will be required to submit recommendations to Congress for changing the maximum amount in the Fund.
- Formation of a scientific management review board to review the NIH organizational structure at least every 7 years and to recommend organizational changes as needed. In addition, the Reform Act specifies a public process for NIH reorganization.
- Authorization of an increase in the NIH budget for each of the next 3 years. This is not synonymous with the appropriation, which is the purview of the Congressional Appropriations Committees.
- Requirement that all grant applications undergo Council review; Council review was previously reserved for applications requesting over $50,000 in direct costs.

Staff Transitions and New Appointments

Dr. Pettigrew announced that several NIBIB staff have transitioned to other positions: **Dr. Alan McLaughlin** was appointed as Director of the Division of Applied Science and Technology. Dr. Pettigrew acknowledged previous interim Director **Dr. John Haller** for his service in this capacity and announced that he is now Liaison for International Activities of the NIBIB.

A number of new staff have joined the NIBIB:

- **Dr. Zohara Cohen** as the Program Director for Biomedical Informatics in the Division of Discovery Science and Technology;
- **Ms. Pamela Glikman** as an Assistant for Council in the Office of Research Administration;
- **Dr. John Hayes** as a Scientific Review Administrator in the Office of Scientific Review;
- **Dr. Lori Henderson** as the Program Director for Biomaterials, Drug and Gene Delivery, and Medical Devices in the Division of Discovery Science and Technology;
- **Dr. Rosemarie Hunziker** as the Program Director for Tissue Engineering and Regenerative Medicine in the Division of Discovery Science and Technology;
- **Dr. Albert Lee** as a Health Scientist Administrator in the Office of Extramural Research;

- **Dr. Xiao-Zhong (James) Luo** as a Health Scientist Administrator in the Office of Extramural Research;
- **Dr. Karen Peterson** as a Senior Advisor to the NIBIB Director; and
- **Ms. Katie Serrano** as a Biomedical Engineer in the Division of Discovery Science and Technology.

NIBIB Quantum Grant Awardee

The first NIBIB Quantum Grant has been awarded to co-Principal Investigators **Dr. Karen Hirshi**, Baylor College of Medicine, and **Dr. Robin Lovell-Badge**, National Institute for Medical Research in London. The goal for the Quantum Grant is to engineer a neurovascular regenerative unit designed to improve neurological function in patients who have suffered focal neurological injuries, such as stroke. The regenerative unit will be developed and grown *ex vivo*, for implantation into the damaged cortex of these patients. In the first phase of the study, the investigators will create a mouse model to study the microvascular and neural stem cell niche environment. This information will be used to engineer the neuro-vascular regenerative unit. An NIBIB delegation recently visited with the team at Baylor College of Medicine, and will continue to have close contact with the team.

Scientific Workshops

The NIBIB continues to host a number of scientific workshops, and Dr. Pettigrew highlighted the following:

- *Imaging as a Biomarker: Standards for Change Measurements in Therapy*. This landmark workshop was supported by a number of Federal agencies and professional societies and hosted by NIST in September 2006. Over 250 scientists and key industrial representatives attended the workshop to discuss biomarker measurements, sources of physical measurement variability associated with image data collection and analysis, and standards for measurements. The workshop also featured open-source software to propagate use of biomarkers and development of tools for evaluating and assessing biomarkers. Several follow-up meetings are planned, and the full report from the initial meeting is available online at http://usms.nist.gov/workshops/bioimaging.htm.
- *Annual NIBIB Grantee Meeting*. Since the NIBIB issued its initial round of requests for applications (RFAs), grantees of the first 10 NIBIB RFAs have met annually to report on their research. Highlights from their reports are featured below (D. Scientific Highlights).

C. Scientific Initiatives

Requests for Applications

The NIBIB reissued an RFA on November 27, 2006, R01 applications for Quantum Project Exploratory Grants. Prior to the receipt date, the NIBIB held a well-attended Webcast/teleconference to review project objectives with potential applicants. Dr. Pettigrew reported positive feedback from the participants, who numbered over 70.

Other new RFAs for which receipt dates have recently passed include those focused on the Point-of-Care Technologies Research Network (U54) and Technology Development of Image-Guided Interventions: Phase 1 (R21). A third RFA on Neuroimaging Informatics Software Enhancement for Improved Interoperability and Dissemination (R03), funded through the NIH

Blueprint for Neurosciences Research framework, is designed to enhance cooperative activities among the NIH Office of the Director and 15 ICs that support research on the nervous system. The NIH has established an independent Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) for facilitating the dissemination and use of existing neuroimaging informatics tools and resources developed through the support of these 15 ICs. In conjunction with the development of the NITRC, supplemental funding will be provided to applicants by the NIH Blueprint for Neuroscience Research for modifying, documenting, and making existing neuroimaging informatics tools and resources more interoperable, usable, and available to the research community. This particular RFA is led by the NIBIB and will involve a total of $1.8 million in administrative supplements.

Outreach Efforts

The NIBIB continues to host regional grantsmanship seminars, the most recent of which was held on October 31, 2006, in Houston, Texas. This seminar, featuring a mock review, was well received by the 186 attendees. To date, the NIBIB has hosted four such seminars that have attracted researchers from all over the country. Information on hosting a regional seminar is available at
http://www.nibib.nih.gov/nibib/File/Funding/NIBIB_Grantsmanship_host_logistics.pdf.

D. Scientific Highlights

Dr. Pettigrew highlighted the work of four NIBIB-funded investigators:

- **Dr. Claude Lechene**, Harvard Medical School, is using multi-isotope mass spectrometry imaging to study substrate metabolism at high resolution. Resolution on the order of 50 nm is achieved by exciting the surface target with cesium ions and raster-scanning a beam across the surface of the sample; negative ions are then swept into the multichannel mass spectrometer. Dr. Lechene has used this technology successfully to visualize protein metabolism on hair filaments in a mouse's ear.
- At Sunnybrook & Women's College Health Sciences Centre in Toronto, Canada, **Dr. John Rowlands** is developing a low-cost digital radiographic imaging system named the X-Ray Light Valve. This system displays a high-quality digital image on a monitor within 10 seconds of the x-ray and requires no film cassettes. The device is constructed using low-cost technologies from materials that are readily available worldwide and thus is approximately one-tenth the cost of commercially available x-ray machines. These characteristics make it particularly suitable for global clinical application.
- NIH Director's Pioneer Award recipient and NIBIB-funded investigator **Dr. Younan Xia**, University of Washington, is using nanostructures to read and control cell behavior. He has developed gold nanocages that form complexes with enzymes and polymers. Placed within the cell, these nanostructures, which turn signaling pathways on and off in a cell rapidly and reversibly, can be used to study, for example, how the number and location of enzymes impacts apoptosis.
- Through a joint effort between the National Institute of Child Health and Human Development and the NIBIB, investigators from the University of California, Irvine are developing pneumatically powered, exoskeletal robotics designed to assist patients who have lost function due to stroke. The robotics not only assist patient movement but also sense patient feedback (e.g., muscle tone and the extent to which the patient can move

unassisted). Algorithms are designed to incorporate these feedback parameters, and patient-specific programs are devised to allow patients to move independently, providing assistance as necessary.

Discussion

Dr. Pettigrew stated that given the current budgetary challenges facing the NIH and the broad mission of the NIBIB, it is critical to identify key research foci where the NIBIB can make a significant contribution. In his vision for the near future, the NIBIB would focus on the transition from a curative to a preemptive medical paradigm and to personalized healthcare by providing early-state diagnosis technologies and translating them to practical applications. Dr. Pettigrew suggested that the new Point-of-Care Technologies RFA also would support such a focus.

Dr. David Satcher asked Dr. Pettigrew whether he envisions partnering with the National Human Genome Research Institute (NHGRI), as the potential outcomes for the Human Genome Project are early disease assessment and personalized medical intervention. In response, Dr. Pettigrew described the NIBIB involvement in the NIH-wide Genes and Environment Initiative (GEI), established in 2006 to identify the relationship among the environment, the genome, and common disease. A particular challenge of this initiative is finding objective ways to evaluate environmental exposure. To this end, the NIBIB is partnering with NHGRI and the National Institute of Environmental Health Sciences, leaders of the GEI public-private partnership, to develop biosensor and point-of-care technologies. Dr. Pettigrew noted that Dr. Brenda Korte represents the NIBIB on the NIH-wide GEI Coordinating Committee, which is responsible for planning and developing the GEI. Implementation of the GEI will begin with a Genome-Wide Association Study, which is focused on finding genetic variations associated with disease.

Dr. Plant asked how systems biology may be included in the future of the NIBIB. Dr. Pettigrew responded that Dr. Grace Peng, an NIBIB Health Scientist Administrator, is leading an active NIH-wide effort in the area of systems modeling. Dr. Pettigrew also noted that information on the Multi-Scale Modeling Initiative is readily available on the NIBIB Web site, and he anticipates new initiatives to improve modeling activities.

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

A. Council Regulations, Policies, and Procedures

Dr. Anthony 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 for discussions of proprietary or personal information is discussed. To comply with these regulations, the NACBIB meeting is open to the public for all but the review of individual grant applications. Dr. Demsey reviewed the guidelines with Council regarding conflict of interest, confidentiality and lobbying.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for May 16, 2007, at a meeting site to be determined. Dr. Demsey reminded members that the meeting date was changed to eliminate conflict with an international conference. The September Council meeting date also has been changed to Monday, September 17, 2007, so as not to conflict with Rosh Hashanah.

C. Approval of the September 15, 2006, NACBIB Meeting Minutes

A motion was entertained to approve the minutes of the September 15, 2006, NACBIB meeting. The minutes were approved unanimously with no modifications.

D. Other Announcements

Dr. Demsey welcomed four attendees representing scientific association constituencies: Ms. Barbara Dunlavy, Biomedical Engineering Society; Ms. Renee Cruea, Academy of Radiology Research; Ms. Jeanie Kennedy, American Academy of Orthopaedic Surgeons; and Ms. Jennifer Ayers, American Institute for Medical and Biological Engineering.

Dr. Demsey recognized Ms. Carol Fitzpatrick and Ms. Pamela Glikman, who assist with Council meeting logistics.

E. Action Items

Report on Involvement of Humans and Animals in NIBIB Research

At the first NACBIB meeting in January 2003, Council members requested an annual report on the involvement of humans and animals in research supported by the NIBIB; the full report was provided to Council members in their meeting binders. Dr. Demsey summarized the report, noting that the inclusion of human subjects in research at the NIBIB is proportionately half the NIH average, while the proportion of research applications involving animals is slightly lower than the NIH average. One notable change from previous years is that the number of NIBIB applications with animal welfare concerns has dropped by nearly 50 percent, now proportionately near the NIH average.

Dr. Demsey suggested that since the numbers of human subjects and animals in research have remained relatively static over the past 4 years, the report may no longer be necessary. Council approved the elimination of this report from future meetings.

FY 2005-2006 Report on NIBIB Activities to Comply With the NIH Policy on the Inclusion of Women and Minorities in Clinical Research

This mandated biennial report must be provided by each Institute to the Office of Research on Women's Health (ORWH). Dr. Demsey reviewed the data in the report, and Council concurred with sending the report forward to ORWH.

V. Report of the Strategic Plan Implementation Working Group Meeting: Dr. David Dzielak

The Strategic Plan Implementation Working Group met on December 1, 2006, and again in the hours immediately prior to the NACBIB meeting. Acting Chair Dr. Dzielak reported that the full-day session in December included a lively discussion about the Institute's Strategic Plan and NIBIB staff presentations on relevant topic areas in the NIBIB research portfolio. These topic areas included optical imaging, multiscale modeling, multifunctional materials for therapeutic delivery systems, and ultrasound enhanced thrombolytic interventions. The presentations were well received by the Working Group and prompted additional discussion on how to review ongoing programs. The proposal embraced by the group was to evaluate program areas based on knowledge gaps, beginning with the optical imaging area.

The Working Group's comprehensive session also included discussion in the following topic areas:

- Fostering public-private partnerships with industry;
- Maximizing limited funding resources;
- Enabling new investigators;
- Encouraging women and minority applicants; and
- Publicizing the NIBIB.

These discussions focused on the potential for a demonstration project to bridge several scientific areas. Working Group members were asked to suggest new areas of research or emphasis for the NIBIB and submit them by e-mail to Dr. William Heetderks. Dr. Dzielak also invited Council members to do the same.

Another full-day session of the Working Group is tentatively planned for August 2007.

VI. Report of the Training and Career Development Working Group Meeting: Dr. Stephen Williams

Dr. Stephen Williams reported that the meeting of the Training and Career Development Working Group covered three topics: (1) optimizing the balance of NIBIB's training initiatives portfolio, (2) transition of funding responsibility of the Howard Hughes Medical Institute (HHMI)–NIBIB Interfaces Initiative to the NIBIB, and (3) identifying areas of focus for future training and career development initiatives.

The NIBIB training portfolio currently is biased toward institutional training grants but still supports a significant number of individual fellowships. The Working Group concluded that with limited funds available for training, the portfolio should be further shifted toward institutional grants. Dr. Williams explained that because grants such as T32s have a broad impact at the institutional level rather than the individual level, they constitute the most efficient use of funds. The Working Group encouraged NIBIB staff to implement this shift.

Dr. Richard Baird reported to the Working Group on his close involvement with Phase I of the HHMI–NIBIB Interfaces Initiative in preparation for transition of funding responsibility to the

NIBIB in 2009. Dr. Baird's thorough report allayed Council members' concerns about NIBIB's preparedness for supporting Phase II of the Initiative.

Dr. Williams noted that the Working Group's discussion of future training efforts at the NIBIB shared a theme related to concerns about funding new investigators that was reported by the Strategic Plan Implementation Working Group. The Working Group considered how the closing of the Whitaker Foundation may negatively impact bioengineering faculty who relied on the Whitaker Foundation Young Investigators' Award as a key source of support. One suggestion that emerged was to hold a joint meeting of the Training and Career Development and Strategic Plan Implementation Working Groups in 2007 to discuss approaches to avoiding the loss of new faculty due to funding cuts.

An additional topic of discussion at the meeting involved measures to improve the participation of women and minorities in NIBIB-funded research. Working Group members offered several ideas on this topic for NIBIB staff consideration. In future meetings, the Working Group plans to discuss public-private partnerships and increasing the number of NIBIB-funded clinical investigators.

Discussion

Dr. Satcher emphasized the importance of considering issues and concerns around diversity of new investigators in the context of the NIBIB Strategic Plan, particularly in light of the challenging budgetary climate. Dr. Pettigrew responded that while developing the Strategic Plan, Institute staff use a global approach to determine how the NIBIB can most impact the national healthcare agenda, and this approach includes consideration of minority and gender issues. Dr. Belinda Seto added that the NIBIB has partnered with a number of other agencies and foundations to address some of these concerns, including:

- The NIBIB–NSF Bioengineering and Bioinformatics Summer Institutes Program focuses on undergraduate students, a substantial proportion of whom are minority students.
- The University of Maryland Meyerhoff Scholarship Program recruits underrepresented minorities into scientific fields.
- The Biomedical Engineering Summer Internship Program provides a 10-week internship for undergraduate biomedical engineering students in various NIH intramural laboratories.
- The NIH/NIST Joint Postdoctoral Program, a collaborative program with the NIST, supports fellows for 1 year each at the NIST and the NIBIB.

In addition, the NIBIB has aggressively used the minority supplement program and has extended the pay line to fund new investigators.

Dr. Satcher expressed the support for programs that promote diversity will be a priority in the Strategic Plan. Dr. Pettigrew assured Dr. Satcher that health disparities are cited as a focus area in the Institute's Strategic Plan. He nevertheless acknowledged the particular challenge presented by health disparities and stated his desire for the Institute to put forth a measurable effort to reduce them. Dr. Pettigrew proposed that the Council have a focused discussion on this topic He acknowledged Dr. Satcher's expertise in the area of health disparities and invited Dr. Satcher's input to the discussion.

In closing, Dr. Pettigrew solicited Council's input, prior to the Institute's annual report to Congress in April 2007, on potential new strategic areas and priorities for the NIBIB.

VII. Staff Presentation: NIBIB Intramural Research Program Overview, Dr. Richard Leapman

Dr. Richard Leapman was introduced as the first Scientific Director of the NIBIB Intramural Research Program (IRP). The primary goal of the IRP is to unite the multidisciplinary fields of bioengineering, biomedical imaging, life sciences, and physical sciences to provide deeper understanding of diseases that will lead to the development of diagnostic techniques and therapies. The IRP has new, dedicated laboratory space in Building 13 on the NIH campus, which adds 12,000 square feet of laboratory and office space, 35 staff positions, and more than $10 million in equipment. Dr. Leapman's presentation highlighted (A) the Division of Bioengineering and Physical Science (DBEPS), which will soon transfer from the NIH Office of the Director to the NIBIB IRP; (B) the existing IRP research program; and (C) intramural training opportunities.

A. Division of Bioengineering and Physical Sciences

The DBEPS comprises basic biomedical and clinical research. The biomedical sciences groups are studying supramolecular structure and function, dynamics of protein assembly, and complex biological systems:

- **Dr. Leapman's** group has developed a number of nanoscale imaging techniques based on unconventional electron microscopy approaches: (1) new methods of electron tomography to reconstruct cell volume on a nanometer scale; (2) energy-filtered imaging to create elemental maps of cells; and (3) scanning transmission electron microscopy, which can help build models of the supramolecular arrangement of proteins, e.g., Alzheimer's disease fibrils – work co-funded with the National Institute of Diabetes and Digestive and Kidney Diseases (*Science* 2005).
- Another group, led by **Drs. Albert Jin and Paul Smith**, is developing atomic force microscopy to measure the mechanical properties of macromolecular assemblies (e.g., clathrin-coated vesicles in receptor-mediated endocytosis).
- A group under **Dr. Peter Schuck's** leadership is using a combination of biophysical techniques to obtain information about the assembly of macromolecular machines that will be useful for many projects including deducing the oligomeric form of signaling complexes after T-cell activation.

The DBEPS clinical research foci are immunochemical nanoscale analysis and diagnostics, pharmacokinetics and drug delivery, and noninvasive optical imaging:

- **Dr. Terry Phillips** has developed a technique of chip-based immunoaffinity capillary electrophoresis ("lab-on-a-chip") that he is using to study inflammation in head trauma.
- **Dr. Bob Lutz's** group works on modeling drug delivery. He recently conducted a quantitative magnetic resonance imaging study on ocular drug distribution, with support from the National Eye Institute.

B. NIBIB Intramural Research Program

The IRP was established 2 years ago and is composed of the Positron Emission Tomography (PET) Radiochemistry Laboratory and the joint Laboratory for the Assessment of Medical Imaging Systems (LAMIS). The PET radiochemistry laboratory, led by **Dr. Dale Kiesewetter**, has developed a novel PET probe for imaging HER2 receptor–positive breast cancer. Animal studies of the distribution with this probe are currently in progress.

The joint LAMIS is a collaboration between the NIBIB and the Food and Drug Administration (FDA) Center for Devices and Radiological Health. Established by **Dr. Peter Kirchner** (NIBIB) and **Dr. Kyle Myers** (FDA), the LAMIS supports five NIBIB postdoctoral fellows. Ongoing research includes using cone-beam computed tomography to create a detailed phantom image of the heart, which will facilitate study of differences between patients based on gender and other factors; computer-aided immunohistochemical imaging and diagnosis of various cancers; and optimizing detectors by modeling the x-ray transport in the detector.

C. Intramural Training Opportunities

There are currently several IRP-supported programs for postdoctoral fellows: (1) National Research Council Research Associateship Program (an NIBIB/NIST collaboration), (2) NIBIB Clinical Radiology Fellows Program, and (3) Intramural Research Training Award (IRTA). In addition, positions are available for visiting foreign fellows. The Postbaccalaureate IRTA provides an excellent opportunity to interest younger students in pursuing a career in bioengineering. Even undergraduate and high school students can be exposed to research at the NIBIB through the Bioengineering Summer Internship Program.

D. Plans for 2007

One of the goals for the IRP in 2007 is to establish an ad hoc Intramural Working Group to discuss potential new initiatives with NIH scientists such as nanobiotechnology, nanomedicine, and innovative imaging initiatives. The goal of the working group would be to obtain input from NIH investigators on areas of research that are potentially high impact and to ensure that the NIBIB's approach is both collaborative and unique. Dr. Leapman also plans to establish search committees for new principal investigators and a Board of Scientific Counselors to review the IRP. Finally, the NIBIB anticipates occupying a leadership position in the Trans-NIH IRP Imaging Initiative, "Imaging from Molecules to Cells," which was deemed a high-priority initiative at a recent NIH Scientific Directors' retreat.

Discussion

In response to a Council member's question about the Trans-NIH IRP Imaging Initiative, Dr. Pettigrew clarified that an NIH Scientific Leadership retreat was recently held to identify crosscutting initiatives that would benefit all of the NIH intramural programs. Prior to the retreat, various Scientific Directors and other leading scientists proposed over 50 initiatives for discussion. As a result of the meeting, the initiatives were prioritized and reduced to three, one of which is the Trans-NIH IRP Imaging Initiative.

Dr. Satcher expressed his appreciation to Dr. Leapman for identifying the relevance of the research being conducted in the intramural program. In particular, the work with heart imaging has implications for health disparities. It is only within the last 5 years that it has been known that myocardial infarction is more deadly in women than men; and this kind of research could uncover the reason for this disparity.

At the request of a Council member, Dr. Leapman described the number of participants in some of the IRP-supported training programs. Currently, there are approximately 16 participants in the Bioengineering Summer Internship Program and 14 postdoctoral fellows (including 3 clinical radiology fellows and 5 postdoctoral fellows working in the joint LAMIS).

In conclusion, Dr. Leapman said that the IRP training programs require only a modest financial investment but are high yield in terms of the future of NIBIB's research agenda.

VIII. Scientific Presentation: Nanoscale Diagnostics, Dr. Terry Phillips

Dr. Terry Phillips is Chief Immunochemist of the Ultramicro Analytical Immunochemistry Resource (UAIR), DBEPS, Office of Research Services, NIH. He received his Ph.D. in analytical immunochemistry from University College, London, and a D.Sc. from the same institution for research into regulatory pathways of the immune system. His current research interest is analytical immunochemistry at the ultramicro level.

Dr. Phillips opened his presentation by describing the advantages of microanalytic techniques: (1) They are applicable to all types of biological samples (e.g., tissues, cells, fluids), (2) they permit multiple analyte assessments in samples less than 1 µL, (3) they involve relatively short analytical time and possess high sensitivity depending on the detector, and (4) reagent costs per analyte are low. Dr. Phillips further stated that microanalytic techniques are extremely useful on special biofluids and tissues such as eye fluid and internal cytosols. He then introduced microfluidics, a multidisciplinary field that has practical application to the design of systems that use microliter and nanoliter volumes of fluids. Microfluidics, which emerged in the 1990s, is used in the development of DNA chips, lab-on-a-chip, and other technologies. It requires extremely small sample volumes (100–0.05 nL) and facilitates rapid and multiple analyte analysis. The instrumentation is portable and has potential for automation and high throughput. Although applications in the clinical arena have been limited, microanalytic techniques can be broadly applied to the development of minimally invasive sampling, monitoring of disease states and progression, monitoring of surgical procedures, assessment of newborns, development of point-of-care procedures, community screening procedures, and field studies in rural areas and countries. Microfluidics may also be applied to building single-cell chambers to conduct single-cell analysis.

Since its inception 6 years ago, the UAIR has successfully developed microscale and nanoscale apparatus. The program's experimental approach is to develop minimally invasive sampling techniques and apply microfluidic techniques to diagnosis. Development of point-of-care systems is ongoing while development of systems for community and field screening is the ultimate aim.

Minimally invasive approaches are used to collect samples in epidemiologic or field studies. For instance, a variety of analytes, such as hormones, cytokines, electrolytes, drugs, and pesticides, can be measured using a blood spot and a sweat patch. Nevertheless, more invasive techniques are necessary to collect special samples such as cord blood and amniotic, cerebral spinal, synovial, and vitreous and aqueous fluids. To this end, the UAIR invented a microdialysis acupuncture needle, with which 0.1mL samples are collected onto an immunoaffinity capillary electrophoresis (ICE) chip or microfraction collector for analysis. One of the most significant problems with these microcollections is the spectrum of proteins and fluids involved. Thus, there is a need for the development of techniques for extracting serum components that require pg/mL-level sensitivity, such as cytokines and neuropeptides, and concentrating them from complex biological matrices.

Immunoaffinity Chromatography

Immunoaffinity chromatography uses an antibody to isolate a specific analyte from biological fluid. In fact, a single analyte can be isolated from a complex sample based on the antibody specificity used to perform the isolation. Analyte concentration also can be achieved. Other advantages of immunoaffinity chromatography include specific labeling of a bound analyte in situ, immobilization of multiple antibodies, and extremely rapid antigen-antibody binding.

Prior to microfluidics, the approach to immunoaffinity chromatography consisted of building small silica capillary immunoaffinity columns and packing them with antibody-coated glass beads. The columns were placed in sequence to achieve recycling analyte capture; i.e., the first column captures one analyte, the unbound analyte is applied to a second, which captures another antigen, etc. Analytes can be differentially eluted into a fraction collector and, using high-performance liquid chromatography, cytokine profiles derived. This approach has been used to develop cytokine and neuropeptide profiles to assess immune function, specifically, immune responses in newborns and vaccine success in infants, to discern neurogenic versus classical inflammatory responses, track the release of inflammatory markers over treatment time, and monitor neuropeptides that are indicative of local pain and inflammation during acupuncture treatment.

Immunoaffinity Capillary Electrophoresis (ICE) Chip

The ICE chip was designed by UAIR, is commercially made, and can be combined with a laptop to create a portable microanalytic device. The ICE chip can analyze neuropeptides in 100 nL of cerebral spinal fluid (CSF) in 120 seconds. It also can determine the degree of inflammation in a single tear from a person with conjunctivitis.

A lab-on-a-chip developed by the UAIR analyzes 50 nL samples in 200 seconds. Antibody labeling can be done during separation, as opposed to prior to analysis, resulting in greater intensities, and the same profiles are obtained using at least half of the original material required by other designs. Using this microchip, Dr. Peter Lipsky, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and collaborators looked at the recovery of neuropeptides from synovial biopsies while preserving the needle biopsy. Samples were extracted from microdissected areas within a 6-micron frozen section. Both the lesion area where the infiltration of the polymorphonuclear cells was located and the actual background within that same patient

(located 5 mm away from the lesion) were analyzed, effectively using the same patient as his or her own normal control.

Another microanalysis application using biospecimens involves the measurement of in situ neuropeptide expression by differential serial biopsies to show how different neuropeptides correlate with pain. In this particular study, it was shown that substance P- and calcitonin-gene related peptide levels increase from onset of pain through mild, moderate, and severe pain while levels of neuropeptide Y and vasoactive polypeptide, known healers and neuroprotectors, rise as remission begins.

To further demonstrate the potential of the ICE chip, the instrument was introduced into the George Washington University hospital emergency room to analyze CSF from patients with head trauma. Micro-CSF taps were taken from patients and cytokine profiles generated within a few minutes. In turn, profiles were correlated with (1) good prognosis and minimal hospital stay or (2) poor prognosis and long hospital stay or death.

Lab-on-a-Chip Flow Immunoassay

To decrease analysis time, UAIR designed a flow immunoassay chip (constructed by a Dutch company) that attaches to a pico pumping system. This chip is capable of detecting neuropeptides in 100 pL of CSF. The apparatus, used to conduct an electrokinetic immunoassay for parathyroid hormone during surgery, successfully measured parathyroid hormone levels during surgery in a period of 5 minutes, significantly reducing the time of surgery.

Dr. Phillips concluded his presentation by listing impediments to nanoscale research at the NIH:

- Lack of onsite microfabrication facilities;
- Use of commercial microfabrication sites—yielding a single chip can take up to 4 months;
- Restricted time available to build chips at the NIST; and
- Need for more in-house expertise.

He added that the latter is the most significant limitation and that education programs in microscale analysis are needed to involve young investigators and spur the use of these applications in communities and the field.

A Council member inquired whether industrial collaborations had been considered to overcome some of the obstacles mentioned. Dr. Phillips replied that a few companies have been supportive, but the microfabrication of these chips is time intensive and is performed on a fee-for-service basis. Establishing partnerships with microfabrication sites, including some located in universities, would be important.

Another Council member asked about what must be done to ensure that microsamples or nanosamples are representative of the factors being measured. Dr. Phillips stated that, currently, nanoscale immunodiagnostics are run in parallel with standard techniques. More work remains to be done to standardize sampling techniques before nanoscale immunodiagnostics become reliable and can be used in the clinical setting.

IX. Approval of Council Operating Procedures

After consideration of the utility of the periodic report of staff administrative actions taken each Council round, Council members acknowledged their desire to continue receiving these reports. Consequently, the Council Operating Procedures were approved with the deletion of the requirement for an annual report on human subjects and animals, but retention of the report on administrative actions.

X. NIH Reform Act of 2006

Council continued discussion of the budgetary implications to the NIBIB of the NIH Reform Act of 2006. A particular concern was how potential increases in the Common Fund might impact on NIBIB's ability to support investigator-initiated research. Council decided to form a Working Group to address this issue and provide advice to the NIBIB and NIH Directors. The Working Group includes Drs. Arenson, Ferrara, Richards-Kortum and Satcher, and Dr. Giddens as Chair.

XI. Adjournment

The meeting open session was adjourned at 1:45 p.m.

XII. 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). The closed session was adjourned at 3:15 p.m.

XIII. 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
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 16, 2007, and corrections or notations will be stated in the minutes of that meeting.