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]
September 15, 2006

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 12th meeting on September 15, 2006, at the Residence Inn Marriott 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 1:30 p.m. to 3:30 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. Robert I. Grossman
*Dr. David Satcher
Dr. Stephen A. Williams
Dr. Frank C. Yin

*Ad Hoc Member

Council members absent:
Dr. Rebecca R. Richards-Kortum

Ex officio members present:
Dr. Bruce H. Hamilton, National Science Foundation
Dr. P. Hunter Peckham, Veterans Administration
Dr. James G. Smirniotopoulus, Uniformed Services University of the Health Sciences
Dr. Elias A. Zerhouni, National Institutes of Health

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

Ex officio members absent:
Dr. Michael Leavitt, Department of Health and Human Services
Dr. Anne Plant, National Institute of Standards and Technology
Dr. Andrew Watkins, Centers for Disease Control and Prevention

Executive Secretary:
Dr. Anthony Demsey

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

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
Dr. David George
Ms. Colleen Guay-Broder
Dr. John Haller
Dr. William Heetderks
Ms. Christine Hollingsworth
Ms. Jeanellen Kallevang
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Brenda Korte
Dr. Richard Leapman
Dr. Hector Lopez
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. Roderic I. Pettigrew
Ms. Patty Runyon
Dr. Belinda P. Seto
Ms. Theresa Smith
Ms. Casey Stewart
Ms. Florence Turska
Mr. Matt Wise
Ms. Li-Yin Xi
Dr. Yantian Zhang
Dr. Ruixa Zhou

Other Federal employees present:
Dr. David Brown, Food and Drug Administration
Mr. John Burklow, National Institutes of Health, Office of the Director
Mr. Francis Costello, National Institutes of Health, Office of the Director
Dr. Lori Henderson, National Institute of Standards and Technology
Dr. Albert Lee, National Institute of Standards and Technology
Dr. Kyle Myers, Food and Drug Administration
Dr. Ross Shonat, Center for Scientific Review

Members of the public present for portions of the meeting:
Ms. Jennifer Ayers, American Institute for Medical and Biological Engineering
Dr. Simon Cherry, Center for Molecular and Genomic Imaging, University of California, Davis
Ms. Renee Cruea, Academy of Radiology Research
Dr. Dan Eckstein, Nova Research Company
Ms. Mariana González del Riego, Rose Li and Associates, Inc.
Ms. Masuko Kaufman, Iri Sangyo Shimbun Press
Ms. Amy Lavarola, Rose Li and Associates, Inc.
Ms. Christine Maisano, Iri Sangyo Shimbun Press
Ms. Lily McCutchan, National Capitol Captioning
Ms. Kate Meris, American Association of Orthopaedic Surgeons
Mr. Mark Pak, National Capitol Captioning
Mr. Anthony Quinn, American Society of Mechanical Engineers
Dr. William Sansalone, Georgetown University
Ms. Bethany White, Capital Consulting Corporation

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey called to order the 12th NACBIB meeting. He reminded attendees that since the morning session of the Council meeting was open to the public, comments about applications should be reserved for the closed afternoon session. Dr. Demsey introduced Dr. Pettigrew, who formally welcomed all participants.

II. Opening Remarks: Dr. Roderic Pettigrew

Dr. Pettigrew opened by welcoming four new members to the Council, whose attendance at this meeting is as *ad hoc* members since their appointments have not yet been finalized:

- **Ms. Rebecca Bergman** is Vice President of Science and Technology at Medtronic, Inc., a medical devices company in Minneapolis, Minnesota. Ms. Bergman completed graduate studies in chemical engineering and materials science at the University of Minnesota, where she also taught courses in biomedical engineering. Since joining Medtronic, Ms. Bergman has held scientific and research and development management positions of increasing responsibility. She now leads Medtronic in the advancement of biologically oriented sciences and oversees its materials and biosciences center, the technology knowledge center, and other corporate technology initiatives. She has received several of the company's highest honors, including membership in the

Medtronic Bakken Society, which distinguishes the company's most accomplished scientific investigators and contributors.

- **Dr. Katherine Ferrara** is Professor and Chair of Biomedical Engineering at the University of California, Davis, where she earned her Ph.D. in electrical engineering and computer science. Before joining the faculty at University of California, Davis, she was an associate professor at Cornell University Medical School, an associate professor in the Department of Biomedical Engineering at the University of Virginia, and a principal member of the research staff at the Riverside Research Institute in New York. In addition to her academic appointments, she currently serves as Associate Editor of the Institute of Electrical and Electronics Engineers' Transactions on Ultrasonics, Ferro Electronics, and Frequency Control. Her research area is medical imaging and biomedical signal processing, with a focus on ultrasonics and acoustics. She is currently investigating the use of ultrasound for therapeutic purposes.
- **Dr. Richard Ehman** is Division Chair and Professor of Radiology at the Mayo Clinic in Rochester, Minnesota. He obtained his M.D. from University of Saskatchewan and had fellowships at the University of California, San Francisco, and the Mayo Clinic. Dr. Ehman is past president of the International Society of Magnetic Resonance in Medicine and recipient of that society's highest honor, the Gold Medal. A pioneer in magnetic resonance, Dr. Ehman developed a technique for eliminating artifacts from images as well as a technique known as "navigator echo," which allows a scanner to synchronize with the respiratory motion of a patient.
- **Dr. David Satcher** is Poussaint-Satcher-Cosby Chair in Mental Health and Director of the Center of Excellence in Health Disparities at Morehouse School of Medicine. He received his M.D. and Ph.D. in cytogenetics from Case Western Reserve University. During the Clinton Administration, he served simultaneously as Surgeon General and Assistant Secretary of Health at the Department of Health and Human Services (DHHS). Dr. Satcher's past positions include President of Meharry Medical College and Director of the Centers for Disease Control and Prevention.

Dr. Pettigrew announced the unexpected passing of Mr. Edward Nagy on July 29, 2006. The loss of Mr. Nagy is especially sad for the NIBIB as he was one of the driving forces in enacting legislation to create the Institute in 2000. Since then, he worked tirelessly to support the mission of the Institute on Capitol Hill and with the general public. Mr. Nagy began his career as a history professor at Austin State University and subsequently at the University of Georgia. He then became Press Secretary for Senator Sam Nunn (D-Georgia 1972–1996). Following the Senator's retirement, Mr. Nagy served as Chief of Staff for Congressman Tim Valentine (D-North Carolina 1983–1995) for several terms and directed multiple successful reelections for the Congressman. In 1995, he was appointed Executive Director of the Academy of Radiology Research, and it was in this capacity that he worked to establish the NIBIB. In honor of him and his commitment to biomedical research, the NIBIB has renamed its award for new investigators the Edward C. Nagy New Investigator Award. Dr. Pettigrew asked Council members and the audience to join him in a moment of silence to remember this outstanding individual.

III. Director's Report: Dr. Roderic Pettigrew

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

A. NIBIB Budget

There have been no significant budgetary changes since the May 2006 Council meeting. A minor change in the NIBIB budget for fiscal year (FY) 2006 is a transfer of $204,000 to the DHHS to support efforts related to the Centers for Medicare and Medicaid Services. The budget distribution among centers, other research, training, intramural programs, contracts, research management and support, and the National Institutes of Health (NIH) Roadmap closely aligns with the FY 2005 distribution. Of note, the NIBIB contribution to the Roadmap represents only 0.9 percent of the NIBIB's FY 2006 budget. For FY 2007, the President's proposed NIH budget is $294,850,000. Although the U.S. House of Representatives and Senate have each passed bills on the proposed budgets, it is unlikely that they will develop and enact a conference bill until after midterm elections.

Dr. Pettigrew reviewed the historical growth of the Institute in terms of number of funded grants and budgetary levels. From FY 2002 to FY 2003, NIBIB funding increased by more than 50 percent. Simultaneously, applications to the NIBIB increased by approximately 450 percent, a management challenge that was met successfully by the Institute. Since then, the budgetary level has remained relatively stable, and the NIBIB currently has a portfolio of more than 800 grants.

In FY 2005, the NIBIB enacted a pay plan that resulted in a 20th percentile pay line. However, due to a modest reduction in appropriated funds for FY 2006 as well as an increase in applications, the FY 2006 pay line decreased to the 17th percentile. The new investigator policy provides for a 5-percent increase in the pay line for new investigators for FY 2006, which would result in funding at the 22nd percentile. Due to this policy, approximately 50 percent more new investigators are receiving funding. Dr. Pettigrew reminded the Council that these numbers are preliminary.

B. NIBIB Significant Events

Recent Staff Appointments: The NIBIB has appointed **Dr. Richard Leapman** as its first Scientific Director for the Intramural Research Program. Dr. Leapman previously served as Acting Director of the Division of Bioengineering and Physical Sciences within the Office of Research Services, NIH Office of the Director, and Chief of the Supra-Molecular Structure and Function Resource at the NIH. His accomplished career began with the receipt of a Ph.D. in physics from the University of Cambridge followed by research at Cornell University and the NIH. Dr. Leapman, who has over 100 peer-reviewed publications, has been distinguished with the Burton Medal from the American Society of Microscopy, the Stratton Award from the National Institute of Standards and Technology (NIST), and multiple NIH Director's Awards. He currently serves as Editor of the *Journal of Microscopy* as well as a member of the Argonne National Laboratory Scientific Committee. Dr. Leapman's research focus is the development and

application of quantitative electron microscopy and the application of novel nanoscale imaging methods to solve problems in structural and cellular biology.

Other recent staff appointments within NIBIB are as follows:

- **Dr. John Anderson** joined the Division of Applied Science and Technology as a Program Director in May 2006.
- **Dr. Peter Moy** transitioned from the Division of Discovery Science and Technology to the position of Director of the Office of Strategic Partnership and Evaluation in June 2006.
- **Dr. Ruixia Zhou** joined the Office of Scientific Review as a Scientific Review Administrator in September 2006.

Update on the Howard Hughes Medical Institute (HHMI)–NIBIB Interfaces Initiative: The NIBIB has established a public-private partnership with HHMI to support an interdisciplinary program for training the next generation of scientists. This is a two-phase program. During the first phase (funded by HHMI for a period of 3 years), curricula to train undergraduate students in interdisciplinary science are being developed at 10 selected institutions. Phase II, which will take place between 2009 and 2014 and will be funded by the NIBIB, will provide support to the students and sustain and advance their Phase I training programs. The first meeting with the Program Directors from each institution was held over the summer. Keynote addresses were delivered by HHMI President Dr. Thomas Cech and NIH Director Dr. Elias Zerhouni. The meeting featured plans for evaluation and monitoring as the program transitions from Phase I to Phase II.

Support for New Investigators: There is concern within the NIH and the extramural research community about the increasing age of investigators at the time of their first major independent research award, accompanied by a progressive decrease in the percentage of competing grants that are awarded to new investigators. As a result of an aggressive program targeting support for new investigators, the NIBIB significantly increased its percentage of awards to this cohort between 2004 and 2005. It is anticipated that the 2006 data will show a similar trend. One such new investigator supported by the NIBIB is Dr. Yihua Bruce Yu, University of Utah, who was one of 12 recipients of the 2005 Presidential Early Career Award for Scientists and Engineers.

Awards and Media Coverage: Dr. Pettigrew announced the following awards and media coverage for the NIBIB community:

- Two NIBIB grantees, **Dr. David Walt**, Tufts University, and **Dr. Robert Sah**, University of California, San Diego, have been selected as 2006 HHMI professors. This $1-million award recognizes outstanding scientists who are also outstanding teachers and mentors, and the awards support undergraduate teaching and mentoring.
- Recently retired Council member and grantee **Dr. Carlo De Luca** received the 2006 Tibbetts Award, which recognizes accomplishments of companies where the stimulus of Small Business Innovation Research (SBIR) funding has made an important and significant difference. With the support of an SBIR grant, Dr. De Luca founded Delsys, Inc., which has developed devices to monitor muscular contraction and the motion of

various limb components in an effort to quantify and evaluate interventional therapies in patients with motion disorders and diseases.

- The NIBIB is a finalist for an International Health and Medical Media Award, known as the Freddie Award. This is the second such honor the NIBIB has received for its recently redesigned Web site.
- Dr. Pettigrew appeared as a guest on the August 31, 2006, edition of the Diane Rehm Show. He was invited along with Dr. Anthony Atala, Wake Forest University, and Dr. William Wagner, University of Pittsburgh, to discuss the future of rebuilding and regenerating human tissues and organs.

C. Scientific Initiatives

Strategic Plan: The NIBIB's Strategic Plan, which is now available in print, outlines strategies for the future of the Institute and provides new areas of focus consistent with this strategy such as point-of-care technologies; image-guided, minimally invasive interventions; regenerative medicine; optical imaging/biophotonics/biosensors; large-scale bioinformatics, particularly standardization of data acquisition and access; and interface between the quantitative and life sciences. Dr. Pettigrew emphasized that in addition to these foci, the Institute will continue to support well-established areas such as magnetic resonance. He also noted that at the recent Director's retreat, DHHS Secretary Michael Leavitt called for an initiative to standardize biomedical information and information platforms. The NIBIB has already begun this initiative and is currently hiring skilled bioinformaticians to support this effort.

Quantum Projects Exploratory Grants: Dr. Pettigrew reminded Council members that the Quantum Project Exploratory Grant objective is to produce a profound or "quantum leap" improvement in a selected human health problem through the use of interdisciplinary and emerging technologies. Approximately 80 applications were received in response to this request for applications (RFA), and the funding plan for the award is a topic of discussion in the NACBIB meeting's closed session.

New RFAs and Program Announcement (PA): An RFA has been issued in support of the NIBIB's Strategic Plan in the area of technology development for image-guided interventions, and another has been issued entitled "Bioengineering Approaches to Energy Balance and Obesity" in support of the trans-NIH effort on diabetes. In addition, a PA focused on enabling technologies for tissue engineering and regenerative medicine was issued in August 2006. Dr. Pettigrew noted that this PA will use the new multiple principal investigator (PI) option being piloted at the NIH.

Outreach Efforts: The upcoming regional grantsmanship seminar will be held in Houston, Texas, on October 31, 2006. Information on hosting a 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 two grantees in the strategic focus area of point-of-care technologies:

Dr. Sanford Asher, University of Pittsburgh, has developed photonic crystal sensors for a variety of analytes. He is using Vitros™, one of the sensors he developed, to analyze the level of creatinine in a patient's body fluids. Dr. Asher has demonstrated a highly linear correlation between the level of creatinine detected by the Vitros™ sensor and the level detected through the use of routine technology. This same technology is being applied by Dr. Asher to noninvasive glucose sensing in tear fluid. Embedded in a contact lens, the sensor causes the light refraction to change upon interacting with glucose. The color of the sensor in the contact lens is interpreted using a color scale that correlates to the patient's glucose level.

Shape memory polymers, which coil when heated, are being tested as a tool to remove clots from the carotid arteries of patients with ischemic stroke. The shape memory polymer, initially in a straightened configuration, is advanced through an occlusion. It is heated with laser light, which causes it to coil, and then is retracted to pull back the clot. **Dr. Duncan Maitland** of Lawrence Livermore Laboratories has fashioned a basketlike device from these polymers and successfully conducted his first *in vivo* study to capture and safely remove a clot from a rabbit carotid artery stroke model.

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 DHHS to open Advisory Council meetings to the public except when proprietary or personal information is discussed. To comply with these regulations, the NACBIB meeting is open to the public except for the review of individual grant applications.

In briefing Council members on the guidelines for conflicts of interest and confidentiality issues, Dr. Demsey noted that it is no longer considered a conflict of interest for an individual from a multicampus institution to review applications from another of the institution's campuses. He emphasized the importance of maintaining confidentiality in all settings, formal and informal. Council members were given examples of when these guidelines should be applied.

Council members were also reminded that for the duration of the meeting, they are special Government employees bound by Federal standards of conduct and therefore, not permitted to engage in lobbying activities. However, a recent interpretation of the lobbying guidelines by the U.S. Office of Government Ethics clarifies that the lobbying ban only applies from opening to closing gavels of the Council meeting. If members wish to visit Capitol Hill while in town for Council meetings, they are free to do so as long as it is done before or after the meeting and without any claims of representing either the NIH or the NIBIB.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for January 26, 2007, at Marriott Suites in Bethesda, Maryland. To allow more time for early-morning workgroup meetings, the open session of the

January Council meeting will begin at 8:45 a.m. instead of 8:00 a.m. Dr. Demsey thanked Council members for informing him of an international meeting that conflicts with the originally proposed May 2007 Council meeting date. In light of this, the May 2007 Council meeting date has been moved to May 16, 2007.

C. Approval of the May 19, 2006, NACBIB Meeting Minutes

A motion was entertained to approve the minutes of the May 19, 2006, NACBIB meeting. The minutes were approved unanimously with no modifications.

D. Other Announcements

Dr. Demsey welcomed four individuals representing scientific association constituencies: Mr. Anthony Quinn, American Society for Mechanical Engineering; Ms. Jennifer Ayers, American Institute for Medical and Biological Engineering; Ms. Renee Cruea, Academy of Radiology Research; and Ms. Barbara Dunlavy, Biomedical Engineering Society.

Three notable absences from this Council meeting are Council member Dr. Rebecca Richards-Korum and two *ex officio* members: Dr. Andrew Watkins, Director of the Technology Transfer Office at the CDC, and Dr. Anne Plant, the new NIST representative to the Council.

Dr. Demsey recognized Ms. Carol Fitzpatrick, the NIBIB Community Management Officer, who is assisting with Council meeting logistics.

V. Report of the Strategic Plan Implementation Workgroup Meeting: Dr. Robert Grossman

The Workgroup's meeting consisted of the introduction of new members; election of Dr. Grossman as Chair and Dr. David Dzielak as Chair-elect; and a summary status report provided by Dr. William Heetderks, Director of the NIBIB's Extramural Science Programs. Workgroup members decided to conduct a strategic planning day, tentatively scheduled for December 2006, during which they will consider the Strategic Plan and develop initiatives and programs that may facilitate the mission of the Institute.

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

Dr. Williams opened with the statement that the overall strategy of the NIBIB's Training and Career Development Program is to focus on institutional training, while maintaining a portfolio that is balanced between large and small institutions. One of the challenges of this program is managing the training budget to restrict growth while anticipating future demands. Chief among those future demands is the HHMI–NIBIB Interfaces Initiative, which is expected to absorb a significant portion of the training program budget beginning in 2009.

During the recent Workgroup meeting, Dr. Richard Baird, Director of the Interdisciplinary Training Programs, reviewed the current portfolio with Workgroup members. One of the

primary issues he raised was the NIH policy on tuition caps that has been recently adopted. In addition, he noted that a needs assessment has been initiated to identify the gaps in the training program that need to be addressed by the Workgroup. The NIBIB held several meetings with training program grantees and directors during the summer and received their input on this topic. Dr. Baird also informed the Workgroup that the new investigator career awards are undergoing review, for funding in 2007, and some supplements have been reissued to support diversity. The strategic shift has been to make these awards to independent early- and mid-career investigators as opposed to established PIs.

One of the future goals of the training program is to develop more public-private partnerships such as the current one with HHMI. The Workgroup debated the merits of developing a focused public-private partnership that brings together industry, academia, and the NIH in support of training. Another topic of discussion among the group was the best program to nurture clinical investigators. Although the training program budget is limited, the Workgroup considered options for spending additional funds to support clinical investigators. These topics will be the subject of future review, and the most promising ideas will be presented to the Council for consideration.

Discussion

A Council member commented on the ongoing challenge to interest physicians in clinical research. He asked whether the Workgroup had considered how the new policy limiting medical residents' hours to 80 per week may affect physicians' interest in clinical research. Dr. Baird acknowledged this challenge and responded that training clinical investigators earlier in their M.D./Ph.D. programs may be one solution. He noted that despite the existence of several award mechanisms geared toward clinical investigators, the new investigator career awards are of most interest to basic researchers. Thus, the Workgroup is considering how to tailor this award to clinical investigators. Strategies for a clinical investigator's transition to residency remain to be addressed. Another Council member confirmed that this is an important area of consideration, and he expressed concern that medical students who are heavily involved in research prior to entering residency are at a disadvantage when they emerge from their residency programs because they have not been exposed to research during that time.

VII. NIH in the Post-Doubling Era: Realities and Strategies for the Future:
Dr. Elias Zerhouni

Dr. Zerhouni began his discussion with the observation that many have described the NIH budget as facing a "perfect storm"- growing Federal and trade deficits, post–September 11th defense and Homeland Security needs, hurricane Katrina, and the $7.1 billion needed for preparing the country for a pandemic flu, in addition to uncertain post-doubling effects, a growing focus on physical sciences, and biomedical research inflation outstripping general inflation. Some have argued that the lack of sustained investment in science and education training is undermining U.S. competitiveness. Challenging times, which are cyclical, need to be considered in context, with attention to facts, and addressed with adaptive strategies.

Dr. Zerhouni acknowledged the apparent paradox in the NIH's current budgetary situation: The budget has doubled, but investigators' success rates in obtaining grants have dropped by one third. The following factors are key contributors to this paradox:

- Capacity building at U.S. research institutions and an increase in the number of tenure-track faculty were stimulated by the doubling of the NIH budget;
- Demand for grants surged at the end of the doubling period;
- Budget appropriation increases were below inflation after 2003, even as the cost of grants increased by a factor greater than inflation; and
- Funding at the NIH is subject to budget cycling, which obligates funds in outyears to projects initiated in past years.

The first factor is the most potent because it requires several years for research capacity–building efforts to come to fruition. Thus, the surge in demand for grants peaked as the NIH budget doubling period ended. This led to a supply/demand imbalance, with the result that success rates dropped. Dr. Zerhouni clarified that decreased success rates per application understate the funding rate per applicant because, on average, applicants apply 1.4 times. He also noted that the budget cycling effect will slightly improve the supply/demand ratio in 2007 and beyond; the "recycling" of grants from better funding years will increase the number of grants that the NIH can issue.

Dr. Zerhouni addressed three misperceptions in the research community about what is causing investigator success rates to drop. The first is that the NIH is overemphasizing applied research. This notion is not supported by the data, which show that except for a one-time decrease in basic research funding in 2003 due to increased funding for biodefense research, basic research funding has held steady around 55 percent since 1998. Meanwhile, funding for applied research has averaged approximately 40 percent of the total budget. The second misperception is that the NIH is shifting away from unsolicited research. In fact, the rate for unsolicited research applications has remained fairly stable at over 90 percent of all research project grant funding. The third misperception is that the NIH Roadmap is shifting funds away from the grant pool. Dr. Zerhouni stated that the Roadmap comprises 400 grants and represents only 1.2 percent of the total NIH budget. He further noted the important contributions of the NIBIB to the Roadmap objectives. The Institute's investment in the Roadmap is returned threefold to its biomedical research community. He exhorted the Council to view the Roadmap as creating more opportunities for interdisciplinary institutes such as the NIBIB.

Dr. Zerhouni briefly discussed the increasing age of new investigators at their first independent research award and general discouragement among younger investigator regarding their chances of receiving any funding. The trend toward aging investigators at the time of independent award is not explicitly an NIH phenomenon, as it correlates to the increasing age of faculty at time of appointment to a tenure-track position. In 2004, Institute Directors were asked to focus on initiatives to increase opportunities for this cohort. Dr. Zerhouni commended the NIBIB for its success in increasing the percentage of its funding for new investigators.

There are several key principles that should guide the NIH through this challenging era. The first principle is to protect the NIH's core values and mission, which is the discovery and generation of new knowledge. The primary way to do this is to support a balanced national

biomedical research portfolio. The NIH portfolio and private sector portfolio are complementary in their emphases, with NIH funding emphasizing basic research and the private sector spending more on clinical research. Dr. Zerhouni encouraged public-private partnerships to achieve a balance in these emphases. It is also the role of the NIH to support high-risk, high-impact research. An example is the NIH Director's Pioneer Awards, a highly competitive program to support individuals with untested, potentially groundbreaking ideas.

Protecting the future generation of scientists is the second key principle. The Pathway to Independence Award, initiated in support of this principle, awards 2-year career development awards to postdoctoral students that lead to 3 years of research grant funding, providing the grantee achieves tenure-track status. Supporting the third principle, balancing supply and demand, requires several activities: Adjusting programs, recycling budgets into a larger number of competing grants, prioritizing projects to maintain reasonable investigator-initiated application success rates, maximizing research and development while minimizing costs that do not contribute to the NIH's core values and mission, and enhancing the peer review process.

The fourth principle is proactive communication about investment in the NIH. Dr. Zerhouni explained that when he testifies before Congress, he emphasizes that funding NIH research activities provides an enormous return to society. The scientific community must take a proactive role in broadening the impact of this message to the greater public. Finally, communication about biomedical research and the NIH's role in it should be motivated by the fifth principle, which is promoting the NIH's vision for the future. This vision is a departure from the traditional model of curative medicine administered at high-cost institutions to a new paradigm of medicine that is predictive, personalized, and preemptive, with increased participation by patients and communities.

Dr. Zerhouni concluded that the work of the NIH is fundamentally about transforming medicine and health through discovery. The challenge moving forward is to communicate to lawmakers and the public that this mission is worth sustaining.

Discussion

A member of the Council asked Dr. Zerhouni to indicate what percentage of the translational research arena should be driven through public-private partnerships. Dr. Zerhouni responded that it remains to be seen since there have been an increased number of these partnerships since 2003, starting with the Bill and Melinda Gates Foundation for the NIH partnership on global health. He described a twofold vision for public-private partnerships: (1) to realize the potential of a world where information is exchanged easily; and (2) to focus on embedding translational research within the academic community in settings that encourage industry collaboration. Dr. Zerhouni commented that, by nature, translational research requires more interaction between the public and private sectors. Resolving the need for such interactions with the public's concerns about conflicts of interest will require work at the policy level.

Another Council member asked Dr. Zerhouni to comment on the prospect for future increases in the NIH budget. Dr. Zerhouni replied that these prospects are not encouraging. He noted that the expected one percent NIH budget increase in FY 2006 did not happen, due to the unexpected hurricane Katrina recovery needs. Although there seems to be bipartisan Congressional good

will toward the NIH, some lawmakers have expressed concerns about conflict-of-interest issues at the NIH. There also are lawmakers who want to see a return on the investment of doubling the NIH budget before legislating more budgetary increases. Dr. Zerhouni stated that this return has been realized and needs to be communicated aggressively. He described two essential elements of this communication plan. The first is to change the paradigm that the NIH budget is a subsidy. He believes that investment in the NIH provides perhaps a greater return than any other in the Federal Government. The second is to emphasize that investing in the NIH is a co-investment with the private sector. Funding the NIH is essentially supporting a compact between institutions providing research infrastructure and scientists supported by the NIH. This compact maintains American competitiveness in one of the most defining scientific areas, life sciences.

A Council member referenced concerns expressed by Dr. Zerhouni in the past on the length of time and expense involved in developing new drugs and asked if there have been improvements in that regard. Dr. Zerhouni replied that he would like to see more rapid progress, but it is inhibited by a lack of understanding of complex biological systems. Although identification of targets and compounds has been very successful, it still is not understood why only one out of thousands of compounds succeeds or only one of numerous targets is validated as a way of influencing a disease process. This is illustrated by the successes of multiple drugs in treating diseases for which they were not originally designed. In addition, further gains are needed in understanding biomarkers; Dr. Zerhouni cited the lack of biomarkers for major diseases such as Alzheimer's disease as a critical issue. Thus, the slow pace of drug development is due to a lack of knowledge rather than a lack of funding or commitment.

A Council member sought Dr. Zerhouni's reaction to the notion that Congress views the biological and physical sciences in competition for funding. Dr. Zerhouni acknowledged the concerns that the Government has overinvested in biological sciences to the detriment of the physical sciences. He supports the physical sciences, particularly considering their important interfaces with the biological sciences, and considers the concept of competitiveness a good way to enhance funding to the physical sciences. However, it is not helpful to scientific endeavors in any arena to create "silos" for each branch of science and fund one by limiting support for the other. Universities, which are responsible for integrating scientific research funding, are heavily invested in the biological sciences. Restricting funding for biological sciences to increase funding for physical sciences will have the long-term effect of making the United States less competitive in the life sciences. He proposed that the better approach is to fund the sciences with a view to integration at the university level.

VIII. Staff Presentation: NIBIB-Supported Nuclear Medicine Imaging Research: Dr. John Anderson

Dr. John Anderson, a Program Director in the Division of Applied Science and Technology at the NIBIB, manages the NIBIB's nuclear medicine imaging research portfolio, which he presented to Council as outlined below.

A. Introduction to Nuclear Medicine Imaging

Nuclear medicine imaging comprises positron emission tomography (PET); single-photon emission computed tomography (SPECT); nuclear medicine planar imaging, also known as

"nuclear X-ray imaging;" and bimodal imaging, which combines two modalities into one scanner (e.g., PET and computerized tomography [CT]). Nuclear medicine images provide functional information about subjects that is useful for healthcare or scientific studies (e.g., blood flow rates in subjects in a cardiac study). The basic process in nuclear medicine imaging begins by injecting a subject with a small concentration of a radio-labeled compound, called a tracer, that leads to the emission of photons. A scanner detects the photons and reconstructs images that are maps of the tracer concentration. Of note, SPECT is less expensive and therefore, more widely used than PET.

B. Portfolio Analysis

Currently, the nuclear medicine imaging research portfolio has approximately $18 million in support. Of its 58 grants, 21 will terminate in 2007. The grants in this portfolio are broadly classified into the following research categories:

- Hardware: Instrumentation and electronics
- Software: Development of algorithms to reconstruct images and correct for errors due to attenuation, scatter, etc.
- Evaluations: Studies to determine how the different modalities can be used to answer fundamental questions
- Development and training of engineers, scientists and clinicians for nuclear imaging
- Probes: Development of new and better tracers

The majority of funding is applied to the hardware and software categories, and, with respect to imaging modalities, most funded studies are PET and SPECT projects. There is a developing effort in bimodal imaging, which has almost $3 million in support for FY 2006. Forty of the 58 grants are research program grants, with the remainder being SBIR and STTR (7), training grants (10), and one biotechnology resource center grant.

C. Portfolio Highlights

Animal Imaging, Bimodal Imaging, and Adaptive Analysis: Under the direction of **Dr. Harrison Barrett**, the University of Arizona Center for Gamma Ray Imaging, research foci are hardware, software for image reconstruction, cameras for animal imaging, and SPECT/CT imaging. The center is also working on a concept called adaptive analysis. This concept involves the use of short scans to provide information that is then used to change the parameters of the camera, for instance, modifying the detector configuration or the way the images are reconstructed.

Improvement of PET Detector Technology: **Dr. William Moses**, Lawrence Berkeley National Laboratories, is investigating PET detectors to determine where the most significant gains can be made in improving detector technology. He has determined that this gain will come from modifying the electronics of the detector systems, in particular the analog and digital electronic circuitry in cameras. His goal with these modifications is to achieve a timing resolution of 550 picoseconds (commercial PET timing resolution is 2.5 nanoseconds). This enhanced timing resolution is expected to reduce background noise in images, resulting in better detection of tumors.

Development of Detectors and Electronics for Small Animal PET Scanners: **Dr. Thomas Lewellen**, University of Washington, focuses his research on the development of detectors and

electronics for small animal PET scanners with high resolution. His team is using silicon photomultipliers and experimenting with different material stacking strategies to create high-performing, small aperture PET scanners.

Development of a Clinical Scanner to Sense and Correct Patient Respiratory and Rigid-Body Motion: **Dr. Michael King**, University of Massachusetts Medical School, is working on an improved clinical scanner setup to sense and correct for patient respiration as well as rigid-body movement during scans. Respiration is particularly problematic as it creates errors in an image that can lead to misdiagnosis. His system employs retro-reflective coated spheres on stretchy bands placed around the patient's torso. These markers are detected by an infrared system that is installed next to the scanner so that the image can be corrected for patient movement.

D. Future Directions in Nuclear Medicine Imaging

An important area in the future of nuclear medicine imaging is the development of probes with improved specificity that will provide functional information at the molecular level. Such probes would, for instance, be able to distinguish between different types of cancers. Improvements in quantitative imaging will increase the importance of nuclear medicine in oncology, cardiology, and neurology. With improvements in computing, the translation of state-of-the-art algorithms for image reconstruction and error correction to clinical practice will be more feasible. Finally, improvements in small animal imaging and multimodal imaging modalities such as PET/MRI are foreseen.

IX. Scientific Presentation: PET Imaging Technology: The Past, the Present, and the Future: Dr. Simon Cherry

Dr. Simon Cherry is a professor in the Department of Biomedical Engineering and Director of the Center for Molecular and Genomic Imaging at University of California, Davis. After receiving his Ph.D. in medical physics from the University of London, he worked with a pioneer in PET research, Dr. Edward Hoffman, at the University of California, Los Angeles. Dr. Cherry's research focuses on small animal imaging to develop models of human disease, as well as bimodal imaging and new detector technology.

Dr. Cherry opened his presentation by defining PET as quantitatively and nondestructively measuring the 3-dimensional (3-D) distribution of injected radiolabeled biomolecules (e.g., fluorine-18) *in vivo*. The isotopes accumulate in targeted areas of the body, decay by positron emission, and emit two high-energy photons at 180° separation. After 500,000 or more such annihilation events are detected, the distribution of the positron-emitting tracer is calculated by tomographic reconstruction procedures. These raw data then are reconstructed with algorithms to yield 3-D quantitative images. A large number of radionuclides decay through the process of positron emission and therefore can be used in PET. However, given the relatively short half-lives of many of these radionuclides, only a few have emerged as clinically useful. Radionuclides with longer half-lives also can be used depending on the kinetics of the compound being studied.

Dr. Cherry then described six key technological innovations that contributed to the evolution of PET from the late 1980s into what it is today:

1. Whole body imaging, which led to widespread clinical use in the field of oncology;
2. 3-D PET, which allowed a five-fold improvement in sensitivity;
3. Lutetium oxyorthosilicate (LSO) and related scintillators that dramatically improved spatial resolution, timing resolution, and count-rate performance;
4. Iterative reconstruction using statistically based algorithms, resulting in improved image quality;
5. PET/CT, which improved sensitivity and specificity for lesion detection and harnessed the capabilities of CT for PET attenuation correction; and
6. Small animal imaging, which opened up preclinical imaging and drug development to nuclear medicine techniques and bridged animal models to studies in humans.

Three topics that are generating interest in the PET field today are (1) time-of-flight PET, which had been rejected in the 1980s; (2) PET spatial resolution limitation (approximately 2 mm at best); and (3) multimodality imaging.

Time of Flight. Conventional PET must use a relatively large timing window of 10–12 ns and assumes that two emissions in that window arise from a single decay event. Time-of-flight PET, envisioned in the 1980s, attempted to eliminate this assumption by measuring the arrival of two photons in a much shorter window to reduce positional uncertainty, but the approach was technologically limited. With recent high-sensitivity scintillators and faster electronics, 600-ps emissions can be detected, allowing localization of the event to within a few millimeters.

Improving Spatial Resolution. Several factors determine spatial resolution in PET including positron range, noncolinearity, detector interaction physics (scatter within detectors and spatial distribution of energy disposition), and detector geometry (width and thickness). Positron range depends on the energy of emitted positrons, is isotope dependent (i.e., greater energy positrons result in greater spread of annihilation), and is not controllable with hardware. In actuality, the emitted positron and electron are not precisely colinear and can deviate by up to a quarter of a degree, resulting in spatial uncertainty. This uncertainty is greatest in whole body imaging from a large (80-cm diameter) scanner ring, but if the ring diameter is decreased to12 cm in diameter, the resolution can be improved nearly 10-fold to 260 microns. Dr. Cherry's research group also has developed LSO scintillator panels 0.25-mm thick in an effort to reduce detector scattering and improve spatial resolution, but denser materials are needed. An alternate approach involves semiconductor-based (e.g., CdTe) scintillator panels only a few hundred microns in thickness. This holds great promise for the future, but more dense semiconductors must be developed before realizing this potential.

PET/MRI Integration. PET and MRI integration challenges are threefold: The need for detectors that function in a high magnetic field; field uniformity better than 1 ppm; and radiofrequency interference. The PET/MRI system being developed by Dr. Cherry's research group has the PET scanner inside a magnet to facilitate simultaneous imaging. Although arrays of scintillator elements still are being used, the scintillation light is transported via optical fibers to a silicon-based detector that is unaffected by magnetic fields. This new system is yielding good results with little cross-interference. In the first *in vivo* murine study conducted recently, the PET/MRI scan yielded quality images and proved the feasibility of combined PET/MRI imaging. Of note, Siemens has plans to develop clinical PET/MRI systems for release in early 2007.

For clinical utilization, sensitivity must still be improved. Long axial field-of-view and time-of-flight concepts would improve sensitivity while providing a whole-body PET/MRI scanner for whole-body dynamic pharmacokinetics, radioimmunotherapy, and improved kinetic modeling. To achieve this, progress must be made in the following areas:

- Investment in new detector materials (new scintillators and dense semiconductors);
- New photodetectors (e.g., photodiodes, silicone photomultipliers);
- Fast, parallel electronics that will support the data throughput on the systems;
- Improved theoretical understanding of iterative, faster algorithms;
- Quantitative analysis and better use of the time domain;
- Low-cost detector approaches for clinical PET to extend the field of view to realize whole-body scanners; and
- High-resolution approaches for preclinical PET.

In addition to technical improvements, Dr. Cherry added that the future of PET in biomedical research depends critically on developing a broader range of targeted imaging probes, as well as more academic trainees in radiochemistry because most are leaving academia and taking industrial positions. Finally, pharmacokinetics must be emphasized, and the application of PET should be expanded beyond small molecules to larger biomolecules such as peptides, antibodies, and cells.

Discussion:
A Council member inquired how improvements in hardware to increase sensitivity affect specificity. Dr. Cherry clarified that specificity depends on the probe that is used. However, it is an important factor to consider since the ability to detect disease and quantify a biological process depends on both the instrument's capabilities in terms of the signal-to-noise ratio and the resolution as well as the probe's biological activity and specificity. Dr. Cherry's presentation focused on improvements in sensitivity independent of specificity.

Another Council member asked about the advent of special purpose PET scanners such as breast imaging scanners that use flat-panel technologies. Dr. Cherry replied that the promise of these scanners lies in the advantages of systems with detectors that are closer together, a fact that has driven small animal imaging research. However, since the breast is attached to the body, a large object, there is a significant amount of scatter from nearby organs. The first clinical trial using a dedicated PET system for breast imaging revealed system performance problems, but the clinical results were encouraging. This may bode well for a second-generation system with a resolution of 1–2 mm for breast imaging. Questions over high cost remain, but Dr. Cherry suggested that high-risk subpopulations and patients in whom physicians are trying to differentiate scar tissue from recurring tumors may be appropriate candidates.

In response to an inquiry on how noncolinearity and positron range impact small animal imaging, Dr. Cherry stated that noncolinearity improves in smaller systems and positron range is isotope dependent. Fortunately, the three most commonly used isotopes in preclinical research today (carbon-11, fluorine-18, and carbon-64) have the lowest positron ranges (i.e., they emit positrons that travel a few hundred microns). In cases where isotopes such as iodine-124 are used, a significant resolution challenge exists. However, in cases where the objective is to detect a very small lesion, as long as the probe is highly specific and has very low background so that a

true signal is registered, the resolution need not be the limiting factor; the aim then is not to determine the size, but the presence of a lesion.

X. Adjournment

The open session was adjourned at 12:30 p.m.

XI. Closed Session

This portion of the meeting, involving specific grant application review, was closed to the public in accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6) Title 5, U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2). The closed session was adjourned at 3:30 p.m.

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
Director,
Office of Research Administration
National Institute of Biomedical Imaging and Bioengineering

_____

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

[2] These minutes will be approved formally by the Council at the next meeting on January 26, 2007, and corrections or notations will be stated in the minutes of that meeting.