DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL ADVISORY COUNCIL FOR
BIOMEDICAL IMAGING AND BIOENGINEERING
Summary of Meeting[1]
May 25–26, 2005

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its eighth meeting on May 25, 2005, in Building 45 (William H. Natcher Building), Room E1-2, in Bethesda, Maryland. 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 on Wednesday, May 25, 2005, from 1 p.m. to 5 p.m. and on Thursday, May 26, 2005, from 8 a.m. to 11 a.m. for the review and discussion of program development, needs, and policy. The meeting was closed to the public on May 26, 2005, from 11 a.m. to 5 p.m. for discussion and consideration of individual grant applications.

Council members present:

Dr. Carlo J. De Luca (via teleconference)
Dr. David J. Dzielak
Dr. Janie Fouke
Dr. Robert I. Grossman (via teleconference)
Dr. Linda C. Lucas
Dr. C. Douglas Maynard
Dr. Norbert J. Pelc
Dr. Stephen A. Williams
Dr. Frank C. Yin
Dr. James A. Zagzebski

Council members not present:

Dr. Shirley A. Jackson
Dr. Rebecca R. Richards-Kortum

Ex officio members present:

Dr. Bruce Hamilton
Dr. Vincent L. Vilker
Dr. Andrew Watkins
Dr. Michael Weiner

Ex officio members absent:

Dr. James G. Smirniotopoulos
Dr. Elias A. Zerhouni, Jr.

Executive Secretary:

Dr. Anthony Demsey

[1] For the record, it is noted that members absent themselves from the meeting when the Council is discussing applications (a) from their respective institutes or (b) in which a conflict of interest may have occurred.

NIBIB staff present for portions of the meeting:

Dr. Prabha Atreya
Ms. Cherise Banks
Ms. Pamela Clatterbuck
Ms. Nancy Curling
Dr. Bonnie Dunn
Ms. Angela Eldridge
Ms. Cheryl Fee
Ms. Rajal Ganatra
Dr. David George
Ms. Colleen Guay-Broder
Dr. John W. Haller
Dr. William Heetderks
Ms. Christine Hollingsworth
Dr. Christine A. Kelley
Ms. Mary Beth Kester
Dr. Henry Khachaturian
Dr. Brenda Korte
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Nicholas Mitrano
Dr. Peter Moy
Mr. Aaron Nicholas
Ms. Donna Pearman
Dr. Grace Peng
Dr. Roderic I. Pettigrew
Dr. Belinda P. Seto
Ms. Karen Shields
Ms. Theresa Smith
Ms. Shana Stepp
Ms. Casey Stewart
Dr. Meredith Temple-O'Connor
Ms. Florence Turska
Ms. Stacy Wallick
Dr. Fei Wang
Mr. Elijah Weisberg
Ms. Li-Yin Xi
Dr. Yantian Zhang

Members of the public present for portions of the open meeting:

Ms. Barb Dunlavey, BMES
Ms. Pat Ford-Roegner, AIMBE
Ms. Mariana González del Riego, Rose Li and Associates, Inc.
Ms. Jeanie Kennedy, AAOS
Ms. Molly Laas, Blue Sheet
Ms. Rachel Lecinson, ASU
Mr. Ed Nagy, ARR
Mr. Kentaro Onishi, ARR
Mr. Jason Rivkin, AIMBE
Dr. William Sansalone, Georgetown University

Other Federal employees present:

Dr. Eileen Bradley, NIH/CSR
Dr. Linda Brady, NIH/NIMH
Ms. Mrunal Chapekar, NIST
Dr. Dharam Dhindsa, NIH/CSR
Mr. Tom Johnson, NIH/OD
Dr. Peter Kirchner, DOE
Dr. Albert Lee, NIST
Dr. Weihua Luo, NIH/CSR
Dr. Richard Swaja, DOE
Dr. Tony Wolbarst, EPA

I. Call to Order and Opening Remarks: Dr. Roderic Pettigrew

Dr. Roderic Pettigrew welcomed Council members, guests, and staff to the eighth National Advisory Council meeting, and announced that the open session of subcommittee meetings would be held jointly. He announced the end of a 3-year NACBIB term of service for Dr. Shirley Jackson, Dr. Douglas Maynard, and Dr. Janie Fouke. On behalf of the Institute, Dr. Pettigrew expressed his sincere appreciation for the service these individuals have rendered to the Council. In recognition of their contributions, he presented each of them with a letter from the Secretary of the Department of Health and Human Services, Michael O. Levitt, and a certificate of appreciation. Dr. Pettigrew then introduced a new member to the Council, Dr. David Dzielak, Associate Vice Chancellor for Strategic Research Alliances at the University of Mississippi Medical Center in Jackson, Mississippi.

Dr. Pettigrew also announced the transition of several NIBIB staff members to other organizations. Dr. Meredith Temple-O'Connor, who served as the acting director of the NIBIB Division of Interdisciplinary Training, will be joining NIGMS as a scientific review administrator. Ms. Sandra Talley, who was the principal contact for the NIBIB inaugural Council meeting in January 2003 and who served in the Office of Science Administration, has joined the Department of Transportation as Chief Diversity and Outreach Officer. Dr. Arlene Chiu, Associate Director for Research Administration and previous Executive Secretary of NACBIB, will join the State of California's efforts to pursue stem cell research as Chief Administrator. Dr. Pettigrew introduced Dr. Anthony Demsey, Acting Director of the Office of Research Administration, who will serve as Executive Secretary for NACBIB. .

Dr. Pettigrew reminded Council members to review the future meeting dates and to contact the Executive Secretary with any requests for changes.

September 13–14, 2005
January 24–25, 2006
May 24–25, 2006
September 12–13, 2006

Dr. Pettigrew entertained a motion by Dr. Norbert Pelc to approve the minutes of the January 2005 meeting, which was seconded by Dr. Maynard. The minutes were approved unanimously without modification.

II. Joint Meeting of the Strategic Plan Development and the Training and Career Development Subcommittees – Highlights of Science Program Retreat: Potential Future Directions for NIBIB Divisions

Dr. William Heetderks, Associate Director for Extramural Science Programs, provided an overview of the Science Program Retreat held on April 21–22, 2005. Dr. Pelc attended the meeting as a representative of the Council. NIBIB staff analyzed current portfolios; outlined a 5-year implementation plan; noted areas for collaboration; and identified near-term, high-priority research directions from each program. To achieve the last objective, retreat participants considered several factors including strategic plan goals, areas of opportunity, NIBIB mission relevance, and scientific maturity. Dr. Heetderks introduced Division Directors, Dr. John Haller, Dr. Christine Kelley, and Dr. Meredith Temple-O'Connor, to provide an analysis of their division's portfolio and research opportunities.

Division of Applied Science and Technology (DAST):Dr. John W. Haller, Acting Director

Dr. Haller began his presentation by reviewing research areas currently funded by the DAST. The Optical Imaging portfolio includes optical coherence tomography, fluorescence imaging, and infrared imaging. The Imaging Agent portfolio emphasizes both contrast agent development and molecular imaging agents. Two potential future directions in these two areas were identified:

- Optical coherence tomography (OCT) is prime for translation from the laboratory to *in vivo* imaging. One specific direction could be to develop *in vivo* OCT imaging technologies such as intravascular OCT of vulnerable plaques in arteries.
- Imaging agents that can be activated allow imaging of specific cellular processes, such as enzyme activities and gene expressions. Thus, the development of new "smart" imaging agents that are activated in response to changes in the local biochemical environment might be pursued.

Given that imaging systems (e.g., computerized tomography [CT], Magnetic Resonance Imaging [MRI]) have developed to a point where there is data overload, a potential future direction in the X-Ray, Nuclear Medicine, and Ultrasound programs is to support imaging informatics, computer-aided detection and diagnosis, and visualization tools for biomedical imaging to address data overload.

The Image-Guided Interventions (IGI) program supports development of image-guided intervention devices and tools such as robots and probe tracking devices; specialized imaging hardware and software for image-guided interventions; and specific applications in image-guided surgery or applications in different diseases such as cardiovascular disease or cancer. Two potential future directions for this program were identified:

- In some common life-threatening conditions, time-to-treatment is a critical factor (e.g., stroke, myocardial infarction, trauma). Combining detection, diagnosis, and treatment in a single patient visit would minimize time-to-treatment and enhance the likelihood of patient survival.
- IGI imaging modes need to operate in real time in the operating room. Developing technologies for 4D (real-time 3D) imaging for IGI would address this need.

The final portfolio discussed was the MRI and Electron Paramagnetic Resonance (EPR) program. This portfolio focuses on MRI physiological imaging, MRI spectroscopy, devices, functional MRI, and *in vitro* imaging techniques of solid state Nuclear Magnetic Resonance and EPR. A potential future direction for this program was identified:

- Early detection and characterization of disease is difficult due to poor sensitivity and spatial resolution of imaging tools for internal organs (e.g., pancreatic islet cell imaging, liver cancer). Research in this area could focus on microimaging of internal organs in a clinical setting. This would entail the development of multimodal, image-guided devices with high sensitivity and spatial resolution (e.g., very high frequency [50–200 MHz], very high-resolution ultrasound, OCT, MRI microcoils).

At the conclusion of Dr. Haller's presentation, Council members and Institute staff discussed the potential future directions for the DAST. Council members were pleased to see the DAST emphasis on technology platforms that cross disease boundaries and have application in a broad range of areas. Council members also discussed methods to facilitate translation of new technologies for patient use.

Division of Discovery Science and Technology: Dr. Christine A. Kelley, Director

Dr. Kelley presented a summary of the portfolio of the Division of Discovery Science and Technology (DDST).

The Materials Technologies program includes research and development of new or novel biomaterials (e.g., implantable medical devices, biosensors, drug and gene delivery) that can be used for a broad spectrum of biomedical applications. Research is focused on the design, synthesis, characterization, processing, and manufacturing of these materials, as well as the design and development of devices that are constructed of these materials, and their clinical performance. Two potential future directions for this program were identified:

- The safety and efficacy of implanted devices is limited by surface problems such as the potential for thrombogenicity and biofouling. One specific goal could be to improve interfacial properties of biomaterials that have potential impact across many applications.
- The effectiveness of current drugs can be improved greatly by target delivery to specific cells and tissues. On the gene delivery side, the clinical applications for gene therapy require delivery vehicles that yield high transfection rates with minimal side effects. A potential direction is to leverage emerging nanotechnologies to develop rationally designed drug and gene delivery vehicles.

The Sensors and Lab-on-a-Chip program encompasses research and development on novel signal transduction approaches, molecular recognition, biocompatibility, signal processing, fabrication technologies, actuators, power sources and research and development of BioMEMS, microfluidics, nanoscale technologies, micro-total analysis systems, arrays, and biochips. Two potential future directions were identified:

- Currently, the emphasis in this area is on development of the technology components and testing on ideal but not real samples. A potential future direction for this program could be to support the development of integrated sensors and lab-on-a-chip devices specifically for point-of-care testing.
- There are ongoing needs for improvements in sensitivity, specificity, multiplexing, and throughput in both sensor and lab-on-a-chip devices. In the future, program directors would like to strengthen the enabling technology development program area with an emphasis on high-risk/high-impact research areas such as nanotechnology.

The Tissue Engineering program encompasses research in enabling technologies, engineering methods and designs, biomolecules and cells, biomaterial scaffolds, and tissue engineering therapies. Two potential future directions were identified:

- There are limited tools and technologies currently available. Therefore, future focus should be on the development of enabling technologies for tissue engineering with an emphasis on real-time, non-destructive tools to assess function; computer-aided tissue engineering; and bioreactors and tissue preservation technologies.
- Inaccuracies and high costs are associated with animal studies to predict human response, safety, and efficacy in drug discovery and development. Therefore, a possible future direction is the development of engineered 3D human tissue model systems for basic and clinical research as well as drug discovery and development.

Finally, the Bioinformatics and Computational Biology program supports the development and integration of computational tools and platforms for many of the scientific areas that are supported by the Institute. The NIBIB is ideally suited to carry out the high-risk, long-term goal of the NIH Roadmap for Bioinformatics and Computational Biology: To “deploy a rigorous

biomedical computing environment to analyze, model, understand, and predict dynamic and complex biomedical systems across scales and to integrate data knowledge at all levels of organization." Therefore, two potential future directions are to promote multi-scale modeling in biomedical systems and to promote intelligent systems design, smart modeling analysis, and simulation methods that automatically adapt to changing conditions.

Discussion followed Dr. Kelley's presentation. Council members addressed issues of biocompatibility and suggested that there may be a need to stimulate research in this area. Council members applauded the efforts of NIBIB to seek input from the research community to confirm research needs, existing gaps, and priorities; and to inform the community of the Institute's interests. A Council member also commended the Institute for its extensive outreach to the community, particularly on promoting the development of true bioinformatics platforms.

Division of Inter-Disciplinary Training: Dr. Meredith D. Temple-O'Connor, Acting Director

In her introduction, Dr. Temple-O'Connor reminded the Council that the Division of Inter-Disciplinary Training (DIDT) was a relatively new division created by Dr. Pettigrew soon after he assumed the NIBIB Directorship. Dr. Temple-O'Connor initially looked at training programs across the NIH and relied on input from the community to determine what the training needs were and what training approaches would best address them.

Dr. Temple-O'Connor summarized the DIDT's grant portfolio. The DIDT portfolio is primarily focused on predoctoral, postdoctoral, and career level awards, including individual fellowships (F31, F32); institutional training grants (T32); career awards (K01, K02, K08, K23, K24, K25); and Academic Research Enhancement Awards (AREA) (R15). The largest portion of the DIDT budget supports T32 awards.

Dr. Temple-O'Connor reported a dramatic increase in the number of applications submitted in FY 2005 compared to FY 2004. This is largely due to increasing visibility within the community.

As a result of the DIDT portfolio analysis, four potential future directions had been identified for the training and career development programs.

- Helping young researchers make the transition to independence is critical. A program that specifically addresses the career transition from postdoctoral fellow to a faculty position would serve this need.
- Based on continuous input from the research community, several target areas need to be fed into the "pipeline" of bioengineering and bioimaging researchers. Target areas include high school and undergraduate opportunities, underrepresented populations (i.e., women, racial and ethnic minorities, and economically disadvantaged individuals), and curriculum development through short courses and formal training opportunities for predoctoral fellows and undergraduates.
- The programs should also pursue the development of clinician-researchers by targeting the M.D. "pipeline." This can be accomplished by involving medical students in research, supporting clinical residents, and supporting a clinical fellow supplements program for research experience.

- A desired outcome of NIBIB-supported research is the translation from technology development to the clinic. Attracting quantitative scientists to careers in biomedical research and interfacing clinicians and basic researchers would promote "cross-talk" and fuel multidisciplinary and interdisciplinary research initiatives, which in turn would ultimately speed translation from technology development to the clinic. Strategies to achieve this goal are co-mentoring (e.g., having a physical scientist and a biomedical scientist co-mentor an individual) and joint training (i.e., recruiting both M.D.s and Ph.D.s into the same curriculum and having them rotate through laboratories side by side).

At the conclusion of her presentation, Dr. Temple-O'Connor informed Council members that DIDT will begin a 6-month evaluation of the division's portfolio, which will culminate in a workshop to which NIBIB grantees, Council members, and other members of the community will be invited. The goal of the workshop is to report the results of the evaluation to participants and obtain comprehensive feedback from the community.

In the ensuing discussion, Council members inquired if students supported by institutional training grants were encouraged to conduct internships in industry and whether those experiences were positive. Dr. Temple-O'Connor indicated that DIDT currently supports a few training grants that propose internships in industry, but that since these grants were only recently awarded, it is too soon to evaluate them properly. In response to further Council discussion, Dr. Temple-O'Connor stated that in FY2004, the NIBIB allocated 3 percent of its budget for training, comparable to the NIH average. Council members also discussed the establishment of metrics for success of the interdisciplinary research program.

III. Director's Report: Dr. Roderic I. Pettigrew

Dr. Pettigrew summarized the progress made by the Institute since the January 2005 Council meeting, the budget outlook, significant events, and scientific highlights and initiatives.

NIBIB Budget
The FY 2005 appropriation of $298 million for NIBIB was signed into law prior to the January 2005 Council meeting. About 77 percent of the budget has been allocated to support research project grants (RPGs). Dr. Pettigrew noted that infrastructure support (i.e., research management and support [RMS]) has been maintained at 5 percent, which is approximately the NIH average. The President's budget for FY2006 is $299.8 million, a slight increase over the FY 2005 appropriation.

Dr. Pettigrew reported on the continuous growth in investigator-initiated (non-RFA) applications submitted to NIBIB from FY 2002 through FY 2005.[2] From FY 2003 to FY 2004, the number of applications doubled and increased by another 20 percent between FY 2004 and FY 2005. Dr. Pettigrew considered the data encouraging because they affirm NIBIB's strong identity as a source of research support in the scientific community. However, it also represents a management challenge to support an increasing number of applications with a limited budget. Nevertheless, NIBIB has successfully balanced these competing factors through the

[2] In FY 2003, NIBIB had an overwhelming response from 10 RFAs. NIBIB has not issued RFAs subsequently.

establishment of an aggressive pay plan. As a result of this pay plan, the NIBIB pay line is now very similar to the NIH average.

Dr. Pettigrew provided an update on the NIBIB report requested by the Congressional Appropriations Committee that would delineate "…a 5-year professional judgment budget that would enable NIBIB to grow at an appropriate rate." This request was based on the observation that the NIBIB was created at the end of the doubling period, thus presenting special challenges as growth in NIH funding has slowed. This report has been reviewed and approved by the Office of Management and Budget (OMB) and is being forwarded to Congress.

NIH Director's Retreats
Dr. Pettigrew reported on the March 1 and May 20, 2005, retreats with the NIH Director, which were attended by the NIH Institute and Center (IC) Directors. The first retreat focused on how the NIH could operate more efficiently and to address issues arising during challenging budgetary times. Among the topics explored were balancing corporate- versus Institute-specific priorities, infrastructure and trans-NIH efficiencies, and corporate funding policies. During the May 20 annual IC Directors' budget retreat, participants explored various budget scenarios, NIH-based programs that could be instituted to encourage earlier and more likely funding for new investigators, translational science, and the NIH Roadmap beyond 2009.

The March retreat led to the establishment of the Office of Portfolio Assessment and Strategic Initiatives (OPASI) within the NIH Office of the Director. This Office seeks to evaluate strategically the entire NIH portfolio in an effort to facilitate collaborations resulting in more efficient management and the conduct of the business of the ICs.

Meetings, Briefings, and Workshops
Dr. Pettigrew reported on Congressional Appropriations hearings held in the House and the Senate on March 9 and April 12, 2005, respectively. Congresswoman Anne Northrop (R-KY) asked Dr. Zerhouni about efforts to foster greater interagency collaboration. Dr. Zerhouni cited the conference entitled "Research at the Interface of the Life and Physical Sciences" held on November 9, 2004, that was organized and hosted by NIBIB and the National Science Foundation.

A briefing on image-guided interventions was held on March 10, 2005, at the request of Representatives Jim Ramsted (R-MN) and Anna Eshoo (D-CA), co-chairs of the House Medical Technology Caucus. The briefing was co-organized by Mr. Ed Nagy of the Academy of Radiology Research. Dr. Pettigrew provided a brief overview of relevant NIBIB activities, and three research groups supported by NIBIB made presentations. Dr. James Duncan, Yale University, talked about image-guided surgery for epilepsy; Dr. Bruce Daniels, Stanford University, discussed MRI-guided breast biopsies; and researchers from the Mayo Clinic presented work on focused ultrasound treatment of uterine fibroids. Remarkable testimonials were offered by patients on the impact that the research studies have had on their lives.

The first NIBIB Grantsmanship Seminar, hosted by the Rensselaer Polytechnic Institute (RPI), was held on April 10, 2005. This seminar provided information on the Institute's research and training opportunities to the scientific community (particularly young investigators and

investigators from the engineering and bioengineering disciplines) and the NIH grant application process to improve NIBIB applicant performance in the peer review process. The Grantsmanship Seminar had a greater attendance and reflected greater geographical area representation than expected. In addition, feedback was extremely positive. NIBIB plans to hold similar workshops in other locations in the future.

An NIH Roadmap Retreat was held on April 20, 2005, to review the progress on Roadmap initiatives, including molecular libraries and imaging in which NIBIB plays a lead role along with the National Human Genome Research Institute (NHGRI) and the National Institute of Mental Health (NIMH). At this retreat, there was consensus by IC directors to continue the Roadmap-like process in the future, with periodic evaluation of the initiatives, ultimately to identify those that should be transitioned to IC portfolios as they mature. In addition, a process was identified by which new initiatives could be pursued using Roadmap funds to invest in and jumpstart cutting-edge and critical areas of research.

The NIH Blueprint Initiative

The NIH Blueprint is a trans-NIH initiative similar to the Roadmap process. It is a framework designed to enhance cooperative activities among 15 NIH ICs that support research on the nervous system. The initiative will support projects that cut across multiple institutes in support of advancing research in the neurosciences. Five FY 2005 projects, such as the Gene Expression Nervous System Atlas (GENSAT), have been identified and are being funded by this consortium of Institutes at approximately $30 million per year for a total budget of $150 million for the first 5 years. Other projects are under consideration for FY 2006 such as a neuroimaging project with NIBIB as the lead institute.

Research Highlights

On the subject of improving biocompatibility of implanted sensors in humans, Dr. Pettigrew summarized the work of three NIBIB grantees in this area.

- **Dr. Mark Schoenfisch**, University of North Carolina at Chapel Hill, and colleagues have determined that by coating glucose sensors with soluble grids that have a time-controlled release of nitric oxide, the attachment and accumulation of platelets to the sensors and the development of biofilm from bacterial overgrowth are inhibited.
- **Dr. Jose Joseph**, SRI International, and his colleagues have observed that by constructing a grid-shaped electrode, the attachment of macrophages is inhibited. Size and spacing of these areas play a critical role in the inhibitory effect.
- **Dr. John Frangos**, La Jolla Bioengineering Institute, and his colleagues are researching mechanical properties that inhibit or promote biofouling. They observed that the elastic modulus of some of these implants and the extent to which they match the elastic modulus of the surrounding tissue are important determinant factors of fibrous accumulation and the development of capsules over various biomaterials and sensors. Coating sensors with a material that more closely matches the elastic modulus has been shown to inhibit this kind of activity.

The work of three other NIBIB grantees was highlighted.

- **Dr. Mark Brezinski**, Brigham and Women's Hospital, and his colleagues have begun to address one of the practical problems encountered in prostatic surgery, the transection of

nerves which lead to urinary incompetence and impotence. They are utilizing OCT for microsurgical guidance.

- **Dr. Suvranu De**, RPI, is developing a visually-based virtual operating theater in which surgeons can be trained to improve their surgical skills. To this end, a physics-based technique for real-time computation of soft tissue deformation/reaction forces in surgery is being developed. Visual realism is enhanced by mapping video images of actual surgical scenes onto the models.
- **Dr. Daniel Hammer** and his colleagues at the University of Pennsylvania are developing self-assembled copolymers resulting in polymersomes that allow the attachment of a large number of bioluminescent signaling agents. In turn, these agents increase the sensitivity of molecular imaging to allow the visualization of a relatively deep-lined tumor in a mouse.

Awards and Honors

Lastly, Dr. Pettigrew informed the Council that the following NIBIB offices and staff members have been recently recognized for their excellence and their dedication to the Institute and service to the NIH.

- The Grants Management Office staff received letters of recognition and special recognition and leadership awards for their significant and outstanding contributions to NIBIB and the NIH.
- The Office of Scientific Review was recognized across the NIH campus for the quality of its reviews and citizenship in volunteering to review applications and initiatives for other institutes that have sought assistance.
- The Office of Science Policy and Public Liaison was recognized for its exemplary performance in handling correspondence for the NIH Office of the Director.
- Dr. Christine Kelley and Dr. Richard Swaja were recently inducted into the College of Fellows of the American Institute for Medical and Biological Engineering (AIMBE) as a result of their significant contributions and leadership at NIBIB.
- Dr. William Heetderks received the NIH Director's Award for his contributions to the NIH Neuroscience Working Group.

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

Dr. Demsey summarized the elements of the Government in the Sunshine Act and the Federal Advisory Committee Act that govern all Advisory Council meetings. These Acts require the Department of Health and Human Services (DHHS) to open Advisory Committee meetings to the public, except when proprietary or personal information is discussed. To comply with these regulations, the NACBIB meeting would be open to the public except for the review of individual grant applications scheduled to begin in closed session at 11 a.m. on May 26, 2005. In briefing the Council members on guidelines for conflicts of interest and confidentiality issues, Dr. Demsey emphasized the importance of maintaining confidentiality in all settings, formal and informal. Members were given examples of when these guidelines should be applied and were offered the opportunity to ask questions to clarify any areas of uncertainty.

Because Council operating procedures had not been approved at the January 2005 Council meeting, they were considered for approval at the present meeting. Dr. Pelc made a motion to

approve such operating procedures and Dr. Maynard seconded the motion. The Council operating procedures were approved unanimously without modification.

Dr. Demsey reminded Council members about early en-bloc concurrence procedures. Dr. Pettigrew, as the Council chairman, can select three Council members to act on behalf of the full Council to consider for funding certain portfolios or segments of applications prior to the Council meeting in September so that NIBIB is positioned to make end-of-year awards expeditiously. Due to an unanticipated delay, Council members will be asked to consider Method to Extend Research in Time (MERIT) applications for funding in September rather than May as indicated in the operating procedures. Finally, Dr. Demsey reminded Council members that a quorum is required to conduct business during NIBIB Council closed sessions. He also formally thanked Ms. Shana Stepp, logistics point of contact for Council members, for her efforts in the preparation of the May 2005 Council meeting.

A motion was entertained to approve the minutes of the January 2005 Strategic Plan Development and the Training and Career Development subcommittee meetings. The minutes were approved unanimously without modification.

V. Joint Report of the Strategic Plan Development and the Training and Career Development Subcommittees: Dr. Norbert J. Pelc and Dr. C. Douglas Maynard

Dr. Pelc and Dr. Maynard reported to the Council on the joint Strategic Plan Development and Training/Career Development Subcommittees meeting held the prior afternoon. A retreat with NIBIB staff was held in April 2005, which Dr. Pelc also attended. During this retreat, participants carefully reviewed the Institute's portfolio, conducting a very detailed analysis of currently funded grants and identifying possible opportunities for new areas in which to promote innovative and significant research. During the May 25, 2005, subcommittee meeting, Dr. Haller, Dr. Kelley, and Dr. Temple-O'Connor summarized those accomplishments. The ensuing discussion centered on proposed ideas designed to encourage new initiatives in both research and training supported by the NIBIB. In general, there was uniform concurrence by the joint subcommittee on potential research areas to be pursued. However, the area of interdisciplinary training generated more discussion. Dr. Pelc concluded his report by stating that the joint subcommittee encouraged NIBIB to strengthen education efforts with remaining funds.

Dr. Maynard remarked that Dr. Temple-O'Connor had reported thoroughly on the major themes that the subcommittees believe should be pursued in regard to training. He added that specific training goals should be set across a continuum and metrics should be developed to evaluate whether such goals are being met. Approximately 3 percent of the NIBIB budget is spent on training grants, and an assessment needs to be conducted to determine whether this amount is sufficient to support this extremely important area.

In closing, Dr. Pelc commended the Institute for holding the scientific retreat and encouraged NIBIB to continue doing so on an annual basis. He also recommended that at least one member of the Council participate in future retreats. In addition, he stated that the ideas generated at these retreats should be shared with the respective constituencies to permit ongoing dialogue that ensures the consideration of a broad representation of opinions.

VI. Scientific Presentation — Advances in Drug Delivery and Tissue Engineering: Dr. Robert Langer

Dr. Robert Langer is a professor of chemical and biomedical engineering at the Massachusetts Institute of Technology (MIT). He has published over 800 articles and holds over 500 patents worldwide. Dr. Langer is a recipient of over 130 major awards, including the Charles Stark Draper Prize for engineers and the Lemelson-MIT Prize for invention. Most recently, he was awarded the Albany Medical Prize, the largest annual prize in medicine offered in the U.S.

Drug Delivery

Dr. Langer began his presentation by providing a brief overview of the advent of drug delivery systems. He explained that the field of drug delivery is a new field that is having a major impact on medicine and the economy. Today, there are approximately 30 million people in the U.S. and 60 million people worldwide using these systems, and sales of these products approximated $27 billion in the United States in 2004. Examples of successful drug delivery systems include a nitroglycerine patch (approved in 1982) that delivers a drug for 24 hours, and Norplant (approved in 1991), a slow diffusion delivery system that can deliver a drug for 5 years.

Dr. Langer's involvement in this field began in the early 1970s, when he was asked by Dr. Judah Folkman to isolate angiogenesis inhibitors and develop related bioassays. Thus began the search for a delivery system that would release macromolecules for extended periods of time without causing harm to the subject.

By the late 1970s, the advent of biotechnology and genetic engineering had resulted in the massive development of peptides and proteins, many of which could serve as viable drugs. However, prior to testing of these peptides, a system had to be developed that would deliver them in an unaltered form. Dr. Langer noted that large molecules, such as growth hormone and insulin, faced significant delivery challenges. After 2 years of design and experimentation, Dr. Langer discovered a way to deliver these macromolecules effectively. He made microspheres by dissolving hydrophobic polymers (e.g., ethylene vinyl acetate or lactic glycolic acid copolymer) in organic solvents and protein at a low temperature. These microspheres could be used to release a variety of viable macromolecules.

A few years later, Dr. Langer and his collaborators developed a refined drug delivery system by cutting micron-thin sections of ethylene vinyl acetate copolymer through which macromolecules (as large as 2 million mw) could be released. Imaging studies revealed that these pores were located among tight, winding constrictions, resulting in longer release times. By regulating these pore structures, release time could be altered from a period of a day to over 3 years.

Using this refined drug delivery system as a basis, Dr. Langer developed assays for angiogenesis stimulators whereby a slow-release polymer in the shape of a dot and containing an angiogenesis inhibitor was inserted near a tumor in a rabbit's eye. A sheet of blood vessels would grow over the polymer in the absence of an inhibitor, and avoid the polymer in the presence of one. Other experiments were conducted in this area including *in vivo* studies where aspirin-sized pellets were placed into diabetic rats to lower blood sugar for over 100 days.

By the mid 1980s, start-up companies had promoted the translation of these applications into the clinic. Today, many of these FDA-approved products are based on these principles. Some of these systems are used for the effective delivery of unaltered peptides, such as injections of slow-releasing microspheres containing luteinizing hormone or hormone analogs. These drug delivery methods —as in the case of Risperdal, a drug used to treat schizophrenia— have prevented compliance problems and reduced hospitalizations. Recently, an application for the approval of a 1-month injection treatment for alcoholism was filed with the FDA. Many other applications are currently in clinical trials.

In an effort to overcome the limitations of these systems, Dr. Langer was inspired by the production of microchips to develop a new, "smarter" drug delivery system. With the help of a ceramics expert, he developed a silicon wafer design. Wells in this system are used to store different drugs. The wells are covered with gold and a single volt is applied to selectively release their contents. Adding polymer gel underneath the gold slows down drug release. In addition, drug release from the system can be triggered at any point in time for many years. Today, this ceramic design has progressed to systems made of degradable materials and to different shapes such as injectable rods.

Continuing work in these areas includes developing a programmable wristwatch or pocket-size device that can regulate drug release by telemetry; creating a smarter system by placing biosensors on these chips along with microprocessors and power sources; and transmitting drug delivery information from a chip to a database designed to store medical records permanently.

Dr. Langer emphasized the importance of approaching the development of medical and drug delivery devices from a biomedical engineering and biological standpoint. For instance, although utilizing polyether urethane to make an artificial human heart (as inspired by the flex life of a lady's girdle) was successful, many problems exist with the design, including the propensity to form blood clots. Dr. Langer further illustrated this point by describing the use of polyester sutures that disintegrate over time. Utilizing this polymer in a drug delivery system can result in bulk erosion or a burst of drug release that could be fatal to the patient. To address this problem, Dr. Langer asked different design questions, such as: What should cause the material to degrade? How can surface erosion be regulated? How can the polymer be induced to dissolve quickly? Because all humans have excess water, water was chosen as the catalyst. Water access was restricted by using hydrophobic monomers as building blocks. Finally, labile bonds, such as the anhydride bond, were introduced into the design to speed the rate of disintegration. Ultimately, it was discovered that by changing the ratio of 2 monomer units, the dissolving rate could be adjusted and therefore, the target delivery time could be regulated.

In an effort to bring these drug delivery designs into the clinic to treat glioblastoma multiforme, a fatal disease, Dr. Langer and his collaborators used the toxic drug BCNU to develop a local chemotherapy approach. BCNU was placed in a polymer and locally delivered to the target by physical placement near the tumor. The polymer was surface-degradable to avoid bulk erosion and it also protected the drug from degradation. This treatment has now been approved for recurring and primary glioblastoma as well as for spinal cancer treatment. Surprisingly, the

major impact of this local polymer chemotherapy has not been in cancer, but in the treatment of heart disease where drug-eluting stents help keep a blood vessel open.

Dr. Langer and his colleagues have also influenced the development of improved inhalers. Inhalers are inefficient due to the aggregation of particles in the respiratory pathway, which impedes drug delivery to the lungs. Dr. Langer observed that all existing aerosols were nonporous and had a density equivalent to that of water. To avoid aggregation, Dr. Langer and his postdoctoral students developed large, light aerosols that resulted in less aggregation due to the reduction in surface area. Dr. Langer further explained that drugs delivered by aerosols are cleared rapidly by lung macrophages. By creating larger aerosol particles, the efficiency of macrophage phagocytosis was addressed. Dr. Langer also mentioned that bioavailability studies for insulin and estradiol aerosols have also been conducted. Currently, clinical trials for insulin, human growth hormone, and other key drugs are ongoing.

Tissue Engineering
Dr. Langer also discussed advances in tissue engineering. He described several projects.

In order to overcome the limitations of organ transplantation, Dr. Langer and Dr. Jay Vacanti, Massachusetts General Hospital, developed a cell transplantation strategy. Building on the concept that isolated, dissociated cells (e.g., osteoblasts, chondrocytes, enterocytes) brought into proximity have the ability to re-form structures, they developed a 3D,biodegradable polymer scaffold to support the growth of these cells in a bioreactor. Once critical cell mass and the desired shape are achieved, the structure can be transplanted *in vivo* to create virtually any tissue. Dr. Langer predicted that using computer-aided techniques, this tissue engineering concept would be used in plastic surgery to develop human parts of 98 percent porous, yet strong and compatible polymer foams. At present, a clinical trial is being conducted where cells from patients are grown on the scaffold to make noses. In turn, a minimally-invasive technique such as arthroscopic scraping is currently being used to develop ears.

Dr. Langer further explored the area of minimally invasive surgery in the context of medical devices. He proposed to use a shape memory effect and develop a family of plastics that, under a specific set of conditions (e.g., room temperature), would have a string shape (to allow the object to be inserted through a hole), but that would be converted into a coil under a different set of conditions (e.g., body temperature). In this phase-segregated, multi-block copolymer approach, one block controls the shape of the object at room temperature while the other controls the shape at body temperature. Recently, Dr. Langer and his colleagues published a study demonstrating this same concept using light.

Another tissue engineering concept that could be used in minimally-invasive surgery is the concept of self-tying surgical knots. A loose object introduced into the body at room temperature can be induced to tighten into a knot. To demonstrate this concept, Dr. Langer showed a video of a string polymer that formed a loop at room temperature. Upon contact with water, the polymer tightens into a knot.

The development of a blood vessel was also pursued by Dr. Langer's laboratory utilizing porous 50 percent collagen tubes. To mimic the circulatory system, cells were hooked up to a pump or

bioreactor to create pulsatile radial stress. In further studies, human endothelial cells were derived from human embryonic cells placed on polymers to make new blood vessels.

Dr. Langer showed an example of a skin polymer scaffold that was recently approved by the FDA. To cure a badly burned 2-year-old boy, a polymer scaffold was created with neonatal dermal fibroblasts and placed on the child at the time of injury. Six months later, the child was healed. This procedure is now approved for burn victims as well as patients with diabetic skin ulcers.

Dr. Langer and his collaborators also have developed the idea of creating spinal cord polymer scaffolds. An outer portion of the polymer scaffold or implant is oriented to provide axonal guidance while the inner portion of the implant is seeded with neural stem cells that will develop into nerves. To test this implant, rats were made paraplegic. Over 12 months, rats were implanted with cells, polymer, the experimental implant, or no treatment. Paraplegic animals 100 days after treatment were not able to bear their own weight and their paws were splayed in an awkward fashion. In contrast, the experimental group was able to bear its own weight and their paws were splayed in a much more normal fashion.

Given all his extraordinary accomplishments, Dr. Langer was also asked what accomplishment had the greatest personal meaning. He replied that, although he was very proud of his scientific accomplishments, he was most proud of his students, not only for their achievements in his laboratory, but in academia. He noted that 140 of his students are professors with distinguished careers all over the world and another 150 are very successful in running medical device companies.

VII. Adjournment

The meeting was closed for review of applications at 10:40 a.m.

VIII. 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).

IX. Certification

We certify that, to the best of our knowledge, the foregoing minutes and attachments are accurate and complete.[3]

_____/s/_____

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

_____/s/_____

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

[3] These minutes will be approved formally by the Council at the next meeting on September 14, 2005, and corrections or notations will be stated in the minutes of that meeting.