DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY COUNCIL FOR BIOMEDICAL IMAGING AND BIOENGINEERING

Summary of Meeting[1]
January 23, 2009

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 19th meeting on January 23, 2009, at the Bethesda Marriott Suites in Bethesda, Maryland. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), presided as Council chairperson.

In accordance with Public Law 92–463, the meeting was open to the public from 9:00 a.m. to 12:40 p.m. for review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:30 to 3:00 p.m. for discussion and consideration of individual grant applications.

Council members present:
Dr. Philip Alderson, Saint Louis University, St. Louis, MO
Dr. Ronald L. Arenson, University of California, San Francisco, San Francisco, CA
Ms. Rebecca M. Bergman, Medtronic, Inc., Minneapolis, MN
Dr. Richard L. Ehman, Mayo Clinic, Rochester, MN
Dr. Katherine W. Ferrara, University of California, Davis, Davis, CA
Dr. Don Giddens, Georgia Institute of Technology, Atlanta, GA
Dr. Gary H. Glover, Stanford University, Stanford, CA
Dr. Augustus O. Grant, Duke University Medical Center, Durham, NC
Dr. Percival McCormack, University of Illinois at Chicago, Chicago, IL
Dr. David Satcher, Morehouse School of Medicine, Atlanta, GA

Ex officio members present:
Dr. Anne Plant, National Institute of Standards and Technology
Dr. John McGrath, National Science Foundation
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences

Council members present via conference call:
Dr. Mae C. Jemison, Biosentient Corporation, Houston, TX
Dr. Cherri Pancake, Oregon State University, Corvallis, OR

Ex officio members absent:
VACANT, U.S. Department of Health and Human Services
Dr. Raynard Kington, National Institutes of Health
Dr. P. Hunter Peckham, Veterans Administration
Dr. Andrew Watkins, Centers for Disease Control and Prevention

Executive Secretary:
Dr. Anthony Demsey

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[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.

Also present:

NIBIB staff present for portions of the meeting:

Mr. Angelos Bacas
Dr. Richard A. Baird
Ms. Barbara Cantilena
Dr. Zohara Cohen
Ms. Shirley Coney-Johnson
Ms. Chris Ann Davis
Mr. Jeff Domanski
Ms. Angela Eldridge
Ms. Kathryn Ellis
Dr. Zeynep Erim
Ms. Cheryl Fee
Ms. Shirley Finney
Ms. Carol Fitzpatrick
Dr. David George
Ms. Marie Gill
Ms. Pam Glikman
Dr. Valery Gordon
Ms. Terry Green
Dr. Ruth Grossman
Ms. Jude Gustafson
Dr. John Haller
Dr. John Hayes
Ms. Eunica Haynes
Dr. William Heetderks
Dr. Lori Henderson
Dr. Rosemarie Hunziker
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Peter Kirchner
Dr. Brenda Korte
Dr. Richard Leapman
Dr. Albert Lee
Dr. Guoying Liu
Dr. Hector Lopez
Dr. James Luo
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Larry Morton
Mr. Joe Mosimann
Dr. Peter Moy
Dr. Grace Peng
Dr. Karen Peterson
Dr. Roderic I. Pettigrew
Ms. Monica Reichwein
Ms. Jessica Ryan
Ms. Sonal Sampat
Dr. Belinda P. Seto
Mr. Shaun Sims
Ms. Thomasine Stovall
Ms. Florence Turska
Ms. Li-Yin Xi
Dr. Yantian Zhang
Dr. Ruixia Zhou

Other Federal employees present:

Mr. Brandon Brough, National Institutes of Arthritis & Musculoskeletal & Skin Diseases, NIH
Ms. Roz Gray, Office of Legislative Policy and Analysis, Office of the Director, NIH
Dr. Stephen I. Katz, National Institutes of Arthritis & Musculoskeletal & Skin Diseases, NIH

Members of the public present for portions of the meeting:

Dr. Anthony Atala, Wake Forest University, Winston-Salem, North Carolina
Mr. Benjamin Beeghly, National Capital Captioning
Ms. Renee Cruea, Academy of Radiology Research
Ms. Blair Feldman, Association of Independent Research Institutes
Mr. Rick Hansen, Digicon Corporation
Ms. Allyson Harkey, NOVA Research Company
Mr. Ricardo Henriquez, Event Technology Solutions
Dr. Perry Kirkham, Purdue University, West Lafayette, Indiana
Ms. Virginia Lathrop, Academy of Radiology Research
Mr. Vhic Mata, Event Technology Solutions
Mr. Jason Michelitch, National Capital Captioning
Mr. Jon Retzloff, Association of Independent Research Institutes

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey called to order the 19th NACBIB meeting. He reminded attendees that the morning session of the meeting is open to the public, welcomed attendees, and introduced Dr. Pettigrew, who formally welcomed all participants.

II. Director's Remarks: Dr. Roderic Pettigrew

A. New Members

Dr. Pettigrew welcomed two new Council members, John McGrath and Philip Alderson. Dr. McGrath, the National Science Foundation (NSF) *ex officio* representative on the Council, is currently professor in the Aerospace and Mechanical Engineering Department at the University of Arizona and director of the Chemical, Bioengineering, Environmental, and Transport Systems Division of NSF. He received his B.S. degree in mechanical engineering from Stanford University and his Ph.D. in mechanical engineering at the Massachusetts Institute of Technology. Dr. McGrath is involved in cryo-preservation research, specifically developing processes to preserve signaling pathways and tissue samples that are used for the study and diagnosis of cancer.

Dr. Alderson is a dean of the St. Louis University School of Medicine and a well-known nuclear medicine physician and diagnostic radiologist. His scholarly writings on pulmonary vasculature and diagnosing pulmonary disease are often used in medical school and residency programs. A past president of the Academy for Radiology Research, Dr. Alderson testified before the Senate on behalf of the Academy in support of creating what is now NIBIB. Prior to joining St. Louis University, Dr. Alderson was chair of the Department of Radiology at Columbia Presbyterian Medical Center and the James Picker Professor of Radiology at the College of Surgeons and Physicians at Columbia University. While at Columbia, he championed the integration of bioengineering and radiology. Dr. Alderson received his medical degree from Washington University in St. Louis.

B. New Staff

Dr. Pettigrew introduced Jeff Domanski, NIBIB's new Executive Officer. Mr. Domanski came to NIBIB from the National Institute of Neurological Disorders and Stroke, where he was the Associate Executive Officer.

C. Changes in Meeting Agenda

Mark Smolonsky, who was originally scheduled to provide the Federal Update, was unable to attend the meeting due to a medical emergency; Rosalind Gray presented in his place.

D. Budget Update

There has been no change in NIBIB's budget since the last NACBIB meeting, due to the continuing resolution in place. The appropriations bills put forth by the House and Senate represent a modest increase in the 2008 budget of 4 percent and 2.3 percent, respectively.

E. The New Administration

A number of recurring themes can be seen in the many public presentations and speeches during the Presidential administration transition. A unifying theme is health care reform, with secondary themes of cost-effectiveness, comparative effectiveness, universal access to health care, wellness, need to improve diagnostic ability, and the technology needed to achieve these goals.

F. Significant Activities

Dr. Pettigrew described five significant activities, three specific to NIBIB, and two NIH-wide.

Indo-U.S. Workshop: Low-Cost Diagnostic and Therapeutic Medical Technologies
Held in Hyderabad, India, in November 2008, this workshop followed an agreement signed with the Indian government approximately one year ago to collaborate on developing low-cost diagnostic and therapeutic medical technologies that will be applicable to both countries. During the 2½-day workshop, NIH medical technology grantees and leading Indian physicians and scientists discussed critical needs and opportunities. Two key target technologies were identified: glucose monitors (e.g., low-cost strips or continuous monitoring) and platform technologies for multiple diagnostic tests (e.g., infectious agents, lipid profile, genetic screens). Formal collaboration between the United States and India was strengthened, and numerous partnerships were forged among the scientists.

Health IT: Accessing and Sharing Image Data
Health information technology is another area of focus for NIBIB, specifically the development of infrastructure to improve patients' ability to access and share image data. The Institute's goal is to enable a patient-centric, Web-based methodology that allows patients to access medical data, including images, independent of the images' points of origin, manufacturer equipment, or storage systems. Next steps to address this challenge include the NIBIB-American Board of Radiology Foundation Summit, a multidisciplinary forum to address cost-effectiveness and over-utilization of imaging, scheduled for August 6–7, 2009; and possible sponsorship of demonstration projects that would concretely illustrate the opportunity and the challenges involved in achieving this goal.

Development and Translation of Medical Technologies That Reduce Health Disparities (RFA-EB-09-001)
NIBIB's first 2009 RFA, Development and Translation of Medical Technologies That Reduce Health Disparities, is part of a joint initiative among NIBIB, the National Center on Minority Health and Health Disparities (NCMHD), the National Institute of Mental Health (NIMH), and the National Center for Research Resources (NCRR), to reduce health disparities through development and translation of medical technologies. This Small Business Innovation Research (SBIR) initiative requires a partnership between the small business and an underserved community clinic in an effort to ensure that the technologies developed address the needs intended. The RFA is for $3.4 million over 5 years.

Comparative Effectiveness Research
Recently, Congress has emphasized the need for comparative effectiveness research. Draft legislation is being developed with the goal of rigorously evaluating the impact of options available for treating a given medical condition for a particular set of patients. The Department of Health and Human Services (DHHS), the Agency for Healthcare Research and Quality (AHRQ), and NIH must submit operating plans within 90 days after enactment; operating plans for FY2010 will be due by November 1, 2009. Proposed funding includes $400 million to NIH and $400 million to the Secretary of DHHS, in addition to funding to AHRQ.

Enhancing Peer Review - Implementation of Recommended Actions
Enhancements to the peer review process have been considered and discussed for some time. Many proposed enhancements focus specifically on the reviewer. For instance, reviewer tour of duty is expected to become more flexible, and virtual review processes will be piloted in 2009.

Scoring will change in May 2009. Streamlined applications will receive individual criterion scores. The upper half of applications will receive an overall impact score; the lower half will not receive an

overall impact score, but individual components of the criteria will be scored in an effort to provide feedback to applicants should they decide to revise their applications. The scoring scale will be collapsed into a 9-number scale, from Exceptional (1) to Poor (9); criteria will be scored individually and as a composite.

Applications will be shortened to 12 pages in 2010. New investigator applications will be clustered during review, as will clinical applications. Only one resubmission will be allowed, beginning January 2009.

G. Science Highlights

Two NIBIB grantees, Drs. Jonathan Wolpaw and John Donoghue, were featured in the November 2, 2008, edition of *60 Minutes*. Both scientists conduct research on brain-computer interfaces for paraplegics and quadriplegics, though they have slightly different approaches. Dr. Pettigrew presented a video clip from the show illustrating Dr. Wolpaw's work, which allows users to spell words by looking at letters as they flash on the computer screen. In earlier research, Dr. Wolpaw was able to determine which brain signals correspond to a given intention, correlating the intended movement and the XYZ plane with the activity. He and his colleagues then derived an algorithm to decode the signals and translate them into XY instructions that determine the computer screen display.

III. Federal Update: Ms. Rosalind Gray

Dr. Pettigrew introduced Ms. Gray, Deputy Director of the Office of Legislative Policy and Analysis (OLPA), Office of the Director, NIH. Ms. Gray synopsized the early activities of the 111th Congress. NIH is currently running under a continuing resolution (CR), and an omnibus bill is expected for the nine bills that have not been enacted. This will likely come after action on the economic stimulus package but before the March 6 CR expiration.

NIH is included in various economic stimulus packages. The House stimulus package marks $1.5 billion over 2 years for research, $500 million to fund high-priority repair and improvement projects on the NIH campus, and $1.5 billion through the NCRR for extramural facilities, renovations, and repair; also included is the $400 million for comparative effectiveness research previously noted by Dr. Pettigrew.

There have been several changes on Capitol Hill that may affect NIH:

- Rep. Dave Obey (D-WI) is Chair of the House Committee on Appropriations' Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; the Ranking Republican is now Rep. Todd Tiahrt (R-KS).
- There were no changes to the Senate Committee on Appropriations' Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; Sen. Tom Harkin (D-IA) is Chair, with Sen. Arlen Specter (R-PA) as the Ranking Republican.
- Rep. Henry Waxman (D-CA) is Chair of the Committee on Energy and Commerce; Rep. Joe Barton (R-TX) remains Ranking Republican. This committee likely will focus on health care reform, U.S. Food and Drug Administration (FDA) reform, and environmental issues for the first few months of the session.
- Sen. Edward Kennedy (D-MA) remains Chair of the Senate Committee on Health, Education, Labor, and Pensions (HELP); the Ranking Republican is Sen. Michael Enzie (R-WY). This committee likely will focus on health care reform for the immediate future.

Through its oversight committee, the Committee on Energy and Commerce may ask further questions about extramural conflict of interest. Sen. Charles Grassley, former Senate Finance Committee Chair, is expected to continue scrutinizing this issue.

Comparative effectiveness, health information technology, and nanotechnology research will continue to be prominent issues. Stem cell research continues to be at issue. The new administration is supportive of NIH research in general, but President Obama has not made concrete remarks regarding stem cells.

IV. Review of Council Procedures and Regulations: Dr. Anthony Demsey

Dr. Demsey noted for the record that a quorum was present for the Council meeting and that Council members Drs. Mae Jemison and Cherri Pancake were unable to attend but would join the closed session via teleconference. *Ex officio* members Drs. P. Hunter Peckham and Andrew Watkins were also absent.

Dr. Demsey welcomed visitors and members of the science press. He also welcomed members of scientific society constituencies, including Renee Cruea and Virginia Lathrop of the Academy of Radiology Research and Blair Feldman and John Retzlaff of the Association of Independent Research Institutes.

Dr. Demsey thanked Ms. Carol Fitzpatrick and Ms. Pam Glikman for their meeting planning efforts.

A. Council Regulations, Policies, and Procedures

Dr. Demsey summarized elements of the Government in the Sunshine Act and the Federal Advisory Committee Act that govern all Advisory Council meetings. These Acts require the HHS 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 for all but the review of individual grant applications. Dr. Demsey reviewed the guidelines with Council regarding conflict of interest, confidentiality, and lobbying.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for May 15, 2009, at the Marriott Suites Bethesda in Bethesda, Maryland. Dr. Demsey asked Council members to inform him of major conflicts with upcoming meeting dates.

C. Approval of the September 16, 2008, NACBIB Meeting Minutes

A motion was forwarded and seconded to approve minutes of the September 16, 2008, NACBIB meeting. The minutes were approved unanimously with minor corrections to the paragraph on Dr. Alderson's biography.

D. Approval of the NACBIB Operating Procedures

A motion was forwarded and seconded to approve the NACBIB operating procedures. The operating procedures were approved unanimously with no corrections.

E. Approval of the Biennial Report on Gender and Minority Inclusion in Clinical Trials

A motion was forwarded and seconded to approve the NIBIB Biennial Report on Gender and Minority Inclusion in Clinical Trials, a required report describing measures NIBIB takes to comply with NIH policies on gender and minority inclusion in clinical studies. The report was approved unanimously with no corrections, to be forwarded to NIH's Tracking and Inclusion Committee.

V. Report of Strategic Planning Workgroup

Dr. Richard Ehman updated the Council on the Strategic Planning Workgroup's progress. The Workgroup met just prior to the Council meeting.

The Workgroup reviewed several program initiatives originally slated for 2009 but likely will be moved into 2010. Six initiatives were considered initially, but only three were deemed worthy of further development:

- A pilot program to provide administrative supplements to support bioengineering standards development, presented by Dr. Cohen, would support comparison and pooling of data, interoperability, and other aspects of standards development.
- *Technology Development of Image-Guided Interventions: Phase II, a Continuation*, presented by Dr. Haller, would focus on developing high-impact, minimally-invasive, image-guided medical procedures and require human application. Image-guided biopsy techniques would be eligible. The RFA would be open to applicants with existing programs in this area funded under Phase I of the initiative and to new applicants, and would use the U01 cooperative agreement mechanism. The budget would be approximately $5 million.
- *Multifunctional Systems for Drug and Gene Delivery*, presented by Dr. Henderson, would focus on systems or agents that incorporate both therapeutic ability and functionality related to imaging.

The Workgroup also discussed NIH leadership's request that NIBIB begin promoting development of a national registry of images, with the goal of reducing duplication of imaging procedures, through demonstration projects. Several projects around the country focus on sharing health care information, though not images specifically; some of these programs could be expanded to include sharing of images, such that the images would be available to multiple health care providers.

Discussion
Discussion centered on interoperability, which could be addressed with grant supplements to support advancement of the use of standards, particularly in technologies just being developed. Larger issues of standardization, such as Digital Imaging and Communications in Medicine (DICOM) standards, will require more resources than the initiative presented by Dr. Cohen provides. Staff at the National Institute of Standards and Technology (NIST) expressed enthusiasm at participating..

VI. Report of Training Workgroup

Dr. Don Giddens outlined progress of the Training Workgroup, which met prior to the Council meeting.

Dr. Richard Baird described various aspects of the training portfolio. The first cohort is in the process of coming through the K99/R00 program; four out of five members of the cohort have obtained faculty positions transitioning to R00 awards. Unfortunately, there has been an NIH-wide drop in applications from clinician scientists and diversity applicants.

The undergraduate training program, in a partnership with NSF, includes a summer research experience for undergraduates and first-year graduate students, focused on bioinformatics and bioengineering. Thirteen programs have approximately 15 students each, all of whom are recruited nationally. The program is slated to be phased out in 2009 and 2010, prompting the Workgroup to discuss whether it should be continued and, if so, in what form. Because the program trains students early in their careers, the Workgroup feels that it may factor in increasing applications from

underrepresented minorities. The Workgroup urges NIBIB to make diversity a high priority when revising and/or developing new programs.

There are two components to residency training through NIBIB: supplements that add to institutional training grants for residents to work on NIBIB-funded projects, and institutional training grants directly from NIBIB. NIBIB-specific institutional training grants seem to have been successful, but there has been a quality decline in supplemental grants. The Workgroup discussed changing the management of the program, phasing out the program, and/or creating a new program.

Faculty hiring freezes at many institutions may affect opportunities for young people coming out of the training programs.

Discussion
It might be worthwhile to position some technology training programs as potential stimulus package targets; for example, greater use of medical records will require training.

NIH is in the process of establishing data regarding how many jobs would be advanced or created per research grant on average, in an effort to position NIH for stimulus funds.

NSF is very supportive of the bioinformatics/bioengineering summer internship program and would like to move forward in partnership with NIBIB to develop that program.

VII. NIBIB P41 Program

The P41 Biomedical Technology Resource Center Program supports novel, cutting-edge, multidisciplinary technology research and development targeting a range of biomedical applications and has five components: core projects to develop or improve technologies, collaborative projects to develop new applications for the centers' technologies, service to provide access to the technologies, training for collaborators and service users, and dissemination of the centers' technologies.

The P41 Evaluation Study, a prototype study examining the P41 Program, is intended to develop a program evaluation process. Its driving factors include the current challenging fiscal environment and the need for a process to strategically manage programs and portfolios to optimize resources to achieve NIBIB mission goals.

The evaluation study report contains Biomedical Technology Resource Center information and program statistics using data compiled from annual progress reports. The review focused on P41 program structure and operation, and examined whether the mechanism works as intended as well as areas of improvement, additional metrics, and lessons learned. Panelists were asked to determine whether this information was sufficient for an assessment of the P41 program. Panelists were chosen for scientific expertise as well as knowledge of NIBIB's mission and operation, and include Drs. Arenson, Ehman, Giddens, Norbert Pelc, and Rebecca Richards-Kortum and Ms. Bergman.

Evaluation study findings include:

- In general, NIBIB P41 Centers are functioning well, and the five program goals seem reasonable. The Program covers a wide range of technologies, including magnetic resonance, magnetic bioelectrical devices, bioinformatics, biomaterials, optical imaging, platform technology, tissue engineering, ultrasound, x-ray, mathematical modeling, and nuclear medicine.
- It is probably wise not to target specific technologies for the cores and to keep the process informal; however, drug delivery/interventional techniques are not well represented.

- The Program is unique in having its cores linked to and motivated by collaborations. If and how the technology is used by collaborators and others is a good indicator of a center's success.
- Productivity should trump longevity when assessing core project performance; some new centers have shown very high productivity. There is no apparent strong correlation between center longevity and dissemination, which highlights a possible area for improvement.
- Meaningful measures of what is cutting-edge need to be developed in order to assess center performance; traditional assessment methods (e.g., publications, patents, and licenses) do not accurately assess whether a project is at the cutting edge.
- A need exists for assessment of the ways that budget-mandated cuts to total direct costs of centers may affect output/productivity of centers; productivity should be related to resources.

Panelists were confused by distinctions in criteria between service, dissemination, and training, which share characteristics and can overlap. The definition and scope of each should be clarified for meaningful assessment and accountability of centers. The amount of service and dissemination reported by P41 grantees varies greatly.

A phased transition process may be needed to allow active management of the P41 portfolio due to a limited budget for allocation across programs. The role of P41s should be assessed from a strategic perspective for effectiveness and efficiency. Further study is required to determine how to modify P41s to truly stimulate new technology development and how to integrate evaluation efforts into corporate strategic planning.

Next steps for the P41 Program include restructuring annual progress reports to better assess cutting-edge research and center productivity, especially at renewal. The panel will discuss service, training, and dissemination. Final panel assessments and recommendations will be summarized in a report to be available via the NIBIB's Web site.

VIII. Health Disparities and Cultural Competency

Dr. David Satcher gave an overview of health disparities and cultural competency issues. Healthy People 2010's two goals—increased length and quality of healthy life, and elimination of racial and ethnic disparities in health—have stimulated activities, including Congressional legislation to create the National Center for Minority Health and Health Disparities (NCMHD). In an effort to achieve both goals, Healthy People 2010 examined determinants of health, including access to quality health care, the physical and social environments, and the biology of genetics. Though human behavior accounts for almost half of the variation in outcome, it is also greatly affected by the other determinants.

The Surgeon General's 2001 report *Mental Health: Culture, Race, and Ethnicity* emphasized culture's impact on patient care in terms of how patients manifest and describe illness, how they cope with illnesses, types of stresses experienced in dealing with illness, and whether and when they are willing to seek treatment. Culture also affects clinicians, impacting how patients are diagnosed, kinds of treatments that health care professionals offer to patients, and how services are organized and financed. As the nation becomes more culturally diverse, physicians, nurses, and public health care professionals should be educated to deal with various cultures.

Mental health research has shown that stigma deters treatment. At the individual level, stigma keeps people from acknowledging a problem and seeking help. At the family/community/societal level, stigma keeps people from recommending help or acknowledging the problem. On a policy level, stigma keeps the public and private sectors from addressing problems.

The Surgeon General's Prescription—which calls for regular moderate physical activity, five servings of fruit and vegetables per day, avoiding toxins (tobacco, illicit drugs, abuse of alcohol), responsible sexual behavior, and daily participation in relaxing and stress-reducing activities—emphasizes individual responsibility. However, people's ability to develop positive lifetime habits can be greatly affected by the social conditions in which they live, work, grow, and die. To successfully eliminate disparities, all stakeholders must care enough, know enough, be willing to do enough, and be persistent.

IX. NIAMS-NIBIB Collaborations and Shared Interests

Dr. Stephen Katz, Director of the National Institute of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS) gave an overview of collaborations and shared interests between NIBIB and NIAMS. Dr. Katz is also the official point of contact for interactions between NIH and the National Aeronautics and Space Administration (NASA).

NIAMS supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; trains basic and clinical scientists to carry out this research; and disseminates information on research progress in these diseases. Specific areas of interest include arthritis and rheumatic diseases (systemic autoimmunity), as well as the biology and diseases of bone, muscle, musculosketal system, and skin.

Because many of the NIH Institutes and Centers (ICs) have overlapping interests, there is much interaction among the various directors and program staff. Several funding opportunities have been in existence for years. Multi-agency projects and working groups include the Armed Forces Institute of Regenerative Medicine (AFIRM), the Federal Working Group on Bone Diseases, the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group, an NIH-NASA collaboration to promote biomedical research on the International Space Station, and the Osteoarthritis Initiative.

NIAMS has a strong interest in tissue engineering and regenerative medicine. The Intramural Cartilage Biology and Orthopaedics Branch is directed by Rocky Tuan, who champions training in regenerative medicine and tissue engineering. The Extramural Musculoskeletal Development, Tissue Engineering, and Regenerative Medicine Program incorporates elements of the NIAMS bone biology, cartilage and connective tissue, and orthopaedic research portfolios. Building Interdisciplinary Research Teams (BIRT) awards provide supplements for new collaborations in areas such as autoimmunity (gender and sex factors, systems biology), developmental biology (systems biology), regenerative medicine (immunology), soft tissue biology (imaging technologies), and tissue engineering (developmental biology). The Extramural Clinical Osteoarthritis and Diagnostic Imaging of Bones and Joints Program is concerned with *in vivo* methods for macro- and micro-scale imaging of bones and joints, the skeletal architecture and mechanical properties of bone, bone quality assessment, and developing novel methods for cartilage and joint imaging.

The Osteoarthritis Initiative

NIAMS partnered with the National Institute on Aging (NIA) to create the Osteoarthritis Initiative in an effort to combat osteoarthritis, a major cause of disability in the United States and around the world. The Osteoarthritis Initiative creates research resources to aid in identifying and evaluating biomarkers as candidates for surrogate endpoints for osteoarthritis.

The Initiative involves NIAMS, NIA, NIBIB, NCMHD, National Institute of Dental and Craniofacial Research (NIDCR), National Center for Complementary and Alternative Medicine, and the Office of Research on Women's Health as well as four pharmaceutical companies (GlaxoSmithKline, Merck

Research Laboratories, Novartis Pharmaceuticals Corporation, and Pfizer, Inc.), each of which have contributed about $800,000 per year in the first 7 years.

The Initiative is developing a prospective natural history cohort to be followed for 4 years, collecting data and specimens that researchers can use to evaluate biomarkers and risk factors for knee osteoarthritis onset and progression. Approximately 5,000 persons participate in the cohort, with roughly 20 percent minority participation, spread over four sites. Clinical data are available at http://www.oai.ucsf.edu; imaging data are shipped on portable hard drives.

The Initiative's next iteration is an extension study that will enable further imaging every other year for the next 4 to 6 years. The extension will increase the number and types of disease and patient outcomes across the spectrum of knee osteoarthritis; enhance statistical power for main analyses; provide adequate statistical power for key subgroup analyses (age, race/ethnicity); and enable studies of imaging, biochemical, and genetic biomarkers of the long-term course and outcome.

Biomedical Research on the International Space Station
The International Space Station (ISS), a National Laboratory with a unique microgravity environment that can be applied to health-related research, will be fully operational in 2011. In 2007, NIH and NASA signed a memorandum of understanding that specifies NIH's responsibility to publicize, to the intramural and extramural communities, availability of the ISS as a research environment and give careful consideration through the standard review process to well-developed, investigator-initiated extramural applications and potential intramural activities relevant to space-related health research.

The NIH research will utilize the ISS to study NIH mission-related topics that require this unique microgravity environment. Potential topics for a Funding Opportunity Announcement (FOA) from multiple ICs include basic biological mechanisms in the absence of gravity; combined effects of radiation and microgravity on normal and tumor cells; cell repair processes and tissue regeneration; human physiology and metabolism; pathogen infectivity and host immunity; spatial orientation and visuo-motor performance; synthesis of new therapeutic compounds, including nanotechnology structures; and telemedicine. The FOA is scheduled for release within the next month.

Discussion
It was pointed out that the Osteoarthritis Initiative focuses mainly on magnetic resonance imaging (MRI) of cartilage; the bone portion of the Initiative has not yet begun. Tomography has been utilized to a certain extent. The Initiative is examining whether researchers can, on a mass level, follow people whose disability or pain is correlated with the MR findings, which would then be used as surrogate or biomarkers for following the outcome of patients who receive certain types of treatments. Galactic cosmic rays that reach earth and bone density are two areas of shared interest between NIBIB and NASA.

X. Staff Presentation

Dr. Rosemarie Hunziker, director of the Tissue Engineering and Regenerative Medicine (TE/RM) Program, gave an overview of TE/RM at NIBIB. *Tissue engineering* applies principles of engineering and life sciences to development of biological substitutes that restore, maintain, or improve function. *Regenerative medicine* refers to self-healing through the endogenous recruitment or exogenous delivery of appropriate cells, biomolecules, and supporting structures. Tissue engineering and regenerative medicine share endpoints and goals—to create structures that can be transplanted into an organism to help restore and rebuild function that has been lost to disease or trauma.

NIH has a robust, relatively stable investment in tissue engineering. Five ICs have dedicated a significant proportion of their overall budget to TE/RM: the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); NIDCR; NIAMS; and NIBIB. NIBIB's portfolio has a heavy concentration on developing biomaterials, scaffolding technologies, and engineering methods, but also includes investigations into cell sourcing, data analysis and modeling. By contrast, other NIH ICs with an investment in TE/RM have different concentrations and focus areas. R01 and R21 mechanisms in NIBIB's portfolio have grown as the portfolio has matured. Out of 56 NIBIB awards, 15 awards target vascular and hematopoietic tissues, 13 target no specific tissue, and 14 concentrate on connective tissue. In terms of the technologies employed, 31 awards are looking at building new and innovative scaffolds, and 10 focus on bioreactor technologies.

Dr. Hunziker described several research projects in the NIBIB TE/RM portfolio, to showcase the breadth and depth of the program.

Engineering the Environment for Embryonic Stem Cell (ESC) Development
The NIBIB portfolio is exploring non-chemical means for controlling how human embryonic stem cells perform. Dr. Sean Palecek's (University of Wisconsin) R01 work indicates that a more predictable outcome in differentiation can be obtained if the geometry of the organizing cell mass is restricted through physical containment. Dr. Todd McDevitt's (Georgia Institute of Technology) R21 project examines embryoid bodies, the first differentiation step from cultured embryonic stem cells, by removing cells from those structures and looking for wound-healing properties in the matrices left behind.

Ultrasound Technologies for Fabrication and Monitoring of Engineered Tissue Constructs
Researchers from the University of Rochester are using ultrasound to create functional, 3-dimensional tissue constructs and monitoring their biological and mechanical properties.

Preassembled Network Promotes Efficient Vascularization of Engineered Tissues
Dr. Jay Hoying's work at the University of Louisville uses a computational approach to design vascularization and microvascularization networks that allow better diffusion of nutrients and waste materials through tissue-engineered constructs.

Quantum Projects in TE/RM
The TE/RM portfolio includes two Quantum Projects: Insulin-Producing Cells from Amniotic Stem Cells (Dr. Anthony Atala, Wake Forest Institute of Regenerative Medicine), and Neuro-Vascular Regeneration (Dr. Karen Hirschi, Baylor College of Medicine). The former project will use pluripotent stem cells to generate large numbers of reliable, robust beta cells to treat diabetes, and the latter project attempts to combine aspects of stem cell biology in neural stem cells with understanding about vascular networks and their role in building constructs to treat stroke patients.

Axons Regenerate Across a Spinal Cord Lesion in the Presence of Bioactive Nanostructures
Dr. Sam Stupp (Northwestern University) has shown that labeled axons near the border of a crush injury in the spinal column of a rat do not cross the border of the injury. However, a self-assembling peptide known to have wound-healing properties that is introduced into the spinal cord environment overcomes the natural resistance of the tissue. In addition, the axons present at the crush injury grow through the injury site to the uninjured part of the spinal column. This mechanism offers hope for addressing spinal cord injury, and is one thrust of this Biological Research Partnership (BRP) grant

Biomedical Technology Resource Centers (P41)
Three NIBIB Biomedical Technology Resource Centers are in the TE/RM portfolio: the Tissue Engineering Resource Center at Tufts University, RESBIO at Rutgers University, and the BioMEMS Resource Center at Massachusetts General Hospital.

Trans-NIH and Trans-Agency TE/RM Activities
NIBIB participates in trans-NIH activities including the Systems-Based Consortium for Organ Design and Engineering (SysCODE), an interdisciplinary Roadmap Consortium. NIBIB is the lead NIH agency in the AFIRM initiative (described by Dr. Katz), and is active in MATES (also described by Dr. Katz).

Transforming Regenerative Medicine: An Interdisciplinary Approach
In May 2008, NIBIB hosted *Transforming Regenerative Medicine: An Interdisciplinary Approach*, which resulted in several recommendations regarding fostering transdisciplinary and interdisciplinary efforts in the field:

- Approach the interdisciplinary nature of TE/RM by supporting cross-training of junior investigators to diversify expertise.
- Coordinate biological knowledge and engineering technologies with clinical needs across the span of research and development. Promote more goal-oriented projects.
- Establish a virtual network so all can monitor the state of the technology, translation, and government funding.
- Sponsor a regularly scheduled NIH symposium/workshop highlighting interdisciplinary TE/RM.

XI. Regenerative Medicine: New Approach to Health Care

Dr. Anthony Atala is the W. H. Boyce Professor and director of the Wake Forest Institute of Regenerative Medicine and chair of the Department of Urology at Wake Forest University School of Medicine. He holds an NIBIB Quantum Grant. A pioneer in tissue engineering and regenerative medicine, his work led to the first successful implantation of a tissue-engineered organ, a bladder. Dr. Atala's discovery of the regenerative potential of stem cells from amniotic fluid received attention from the lay and scientific press about a year ago. Dr. Atala is exploring amniotic stem cells as a potential curative therapy for Type 1 diabetes.

Dr. Atala outlined the history of transplantation, beginning with the first organ transplant 55 years ago. Despite many advances in transplantation medicine since then, some of the same challenges—organ rejection and shortage—remain today.

Understanding growth factor biology is essential for expanding normal human cells in large quantities outside of the body. Adding specific growth factors allows human progenitor cells to be expanded outside the body, increasing from a small group one-half the size of a postage stamp to quantities large enough to cover a football field in 60 days. Stem cells are needed to grow sufficient numbers of some cell types (e.g., heart, liver, nerve, pancreas) in vitro.

Another challenge is delivering cells into the body safely in order to engineer tissues or create cell therapy. Dr. Atala uses the concept of a scaffold that replicates the biomechanical and structural properties of the tissue being replaced. Biomaterial scaffolds are designed to allow cells to grow in sheets and provide the porosity necessary to develop neo-vascularization and neo-innervation.

Dr. Atala takes a small piece of a patient's tissue, separates the cells, expands them in large quantities, and regenerates the tissue using scaffolds. One of the first tissues engineered this way was the urethra. If a defect in the tissue is less than 1 cm long and there is a healthy urethral bed, one can use scaffold alone to regenerate the tissue; otherwise, cells must be added to the scaffolds. These technologies also have been used to regenerate blood vessels using peripheral blood-derived progenitor cells that were differentiated into endothelial and smooth muscle cells and then coated onto a tubular scaffold. In a rabbit model, Dr. Atala's team completely replaced vaginal tissue using implanted vaginal epithelial and smooth muscle cells seeded on polymer scaffolds. This regeneration technique is now applied in clinical trials for patients with vaginal agenesis.

The first bladder replacement clinical studies for patients with end-stage bladder disease started in 1999. A small piece of bladder is biopsied and broken down to individual components: muscle cells and urothelial cells. A bladder-shaped scaffold is coated with epithelial cells on the inside and muscle cells on the outside. The scaffold is then placed in an incubator for 6–8 weeks and then implanted into the patient. The scaffold is constructed specifically for each patient, based on 3D CT scans. The patients are now in 8-year followup, and a Phase III clinical study is in progress.

Reconstructing solid organs is a great challenge due to the large number of cells that require increased vascularity. One strategy for solid organs involves washing a porcine liver with mild detergents to remove all the cells, while preserving the vascular tree. The cell-free organ scaffold is then perfused with endothelial and liver cells and implanted into an animal. This technology is still under investigation, but implanted organs show some functionality. Another strategy is to print biological constructs, one layer at a time. Within 40 minutes, a desktop printer programmed with a 3D elevator can construct a 2-chamber heart that starts beating on its own in 4–6 hours. Another approach uses cells without a scaffold, such as in cartilage cell replacement technology, which is currently in Phase II and III multicenter clinical trials.

Cells can be genetically modified to secrete vascular and endothelial growth factors. Injecting such cells increases vascularity. Cells can also be encapsulated into Ca-Alginate beads that allow influx of nutrients and excretion of growth hormones and proteins, while shielding encapsulated cells from the host immune system. This approach has been applied in tumor therapy to stop blood vessel growth.

Until recently, only three populations of stem cells were known to give rise to all tissues: adult bone marrow stem cells, induced pluripotent stem cells (derived from skin), and embryonic stem cells. Rejection problems limit use of embryonic stem cells because the genetic makeup of the embryo is different from that of the host. Unlike embryonic and induced pluripotent stem cells, adult bone marrow stem cells do not form tumors and are not rejected. However, adult bone marrow stem cells cannot be grown in large quantities to generate ectodermal and endodermal cells. Stem cells derived from amniotic fluid and placenta do not form tumors, do not get rejected, and can be grown in large quantities. However, unlike embryonic cells, these stem cells probably will not be able to generate all human tissues.

The NIBIB Quantum Grant program funds Dr. Atala's work using amniotic stem cells to generate pancreatic beta cells in a mouse diabetes model. Upon injection, the stem cells repopulated the pancreas with beta cells that started producing insulin. These cells expressed genes consistent with beta cell lineages (e.g., Pdx-1, Pax-6, Ngn-3, insulin-1, and insulin-2). In collaboration with Camillo Ricordi (University of Miami), the studies have been replicated with human stem cells.

Dr. Atala's preferred approach to repairing small defects is to use scaffolds without cells. When scaffolds alone are not sufficient, one must use cells, preferably a patient's own cells, because those

cells already know what to do, will not be rejected, and are an easy source. If a patient's cells are unavailable or cannot be grown in sufficient numbers, stem cells must be used.

AFIRM represents the first partnership between NIH and the armed services in this area of research. NIBIB is a major contributor to the program, which comprises four major areas: cranio-facial regeneration, burn and scars healing, limb and digit regeneration, and compartment syndromes.

Dr. Atala noted that the work he presented was performed by over 600 researchers across an 18-year time span. Molecular biologists, cell biologists, bioengineers, material scientists, and physicians work together to bring these technologies from bench to bedside. He acknowledged and thanked the funding sources, the NIBIB, and his team.

Discussion

An audience member inquired about the logic behind steering multi-potential cells to differentiate in different directions. Dr. Atala clarified that the growth factor biology for stem cells has been defined but has been difficult to understand for primary human cells. To differentiate, cells must be placed under the same conditions they would be exposed to during embryologic development and use some of the same growth factors.

A Council member asked whether people should bank cells at birth. Dr. Atala noted that people have been saving cord blood cells at birth, but cord blood can be used only for hematopoietic cells, cord blood cells cannot be expanded, and cord blood is good only until the patient is a teenager. After that the patient usually must turn to a donor bank. Banking amniotic fluid and placental cells would be better because these cells keep growing and can be differentiated into many directions. Senator Coleman and Congressman Lipinski have introduced a bill proposing a national stem cell bank from these sources.

XII. Adjournment

The open session of the NACBIB meeting was adjourned at 12:40 p.m.

XIII. Closed Session

The specific grant review portion of the meeting was closed to the public in accordance with 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 3:00 p.m.

Certification

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

_____ Anthony Demsey, Ph.D.

Executive Secretary,
National Advisory Council for Biomedical
Imaging and Bioengineering
Director,
Office of Research Administration
National Institute of Biomedical Imaging
and Bioengineering

_____ Roderic I. Pettigrew, Ph.D., M.D.

Chairperson,
National Advisory Council for Biomedical
Imaging and Bioengineering
Director,
National Institute of Biomedical
Imaging and Bioengineering

[2] These minutes will be approved formally by the Council at the next meeting on May 15, 2009, and corrections or notations will be stated in the minutes of that meeting.