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

NATIONAL ADVISORY COUNCIL FOR BIOMEDICAL IMAGING AND BIOENGINEERING

Summary of Meeting[1]
September 16, 2008

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 18th meeting on September 16, 2008, 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 12:25 p.m. for review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:15 to 3:30 p.m. for discussion and consideration of individual grant applications.

Council members present:
Dr. Ronald L. Arenson
Ms. Rebecca M. Bergman
Dr. Richard L. Ehman
Dr. Katherine W. Ferrara
Dr. Gary H. Glover
Dr. Augustus O. Grant
Dr. Percival McCormack
Dr. Cherri Pancake

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

Council members absent:
Dr. Philip Alderson
Dr. Don Giddens
Dr. Mae C. Jemison
Dr. David Satcher

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

Ex officio members absent:
Mr. Michael Leavitt, U.S. Department of Health and Human Services
Dr. Elias A. Zerhouni, National Institutes of Health

Executive Secretary:
Dr. Anthony Demsey

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

Dr. Prabha Atreya
Mr. Angelos Bacas
Dr. Richard A. Baird
Ms. Sheila Barrett
Dr. Abesh Bhattacharjee
Ms. Barbara Cantilena
Mr. Larry Clark
Dr. Zohara Cohen
Ms. Shirley Coney-Johnson
Ms. Nancy Curling
Mr. Jeff Domanski
Ms. Angela Eldridge
Dr. Zeynep Erim
Ms. Cheryl Fee
Ms. Shirley Finney
Ms. Carol Fitzpatrick
Dr. David George
Ms. Marie Gill
Ms. Pam Glikman
Dr. Valery Gordon
Dr. Ruth Grossman
Ms. Jude Gustafson
Dr. John Haller
Ms. Rosslyn Hart
Dr. John Hayes
Ms. Eunica Haynes
Dr. William Heetderks
Dr. Lori Henderson
Dr. Rosemarie Hunziker
Ms. Orit Jacobson
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Dale Kiesewetter
Dr. Peter Kirchner
Dr. Brenda Korte
Dr. Lixin Lang
Dr. Richard Leapman
Dr. Guoying Liu
Dr. Hector Lopez
Dr. James Luo
Dr. Ying Ma
Dr. Alan McLaughlin
Mr. Todd Merchak
Ms. Carol Morales
Mr. Larry Morton
Mr. Joe Mosimann
Dr. Peter Moy
Dr. Grace Peng
Dr. Karen Peterson
Dr. Roderic I. Pettigrew
Ms. Sonal Sampat
Ms. Katie Serrano
Dr. Belinda P. Seto
Mr. Shaun Sims
Ms. Thomasine Stovall
Ms. Kawannah Taylor
Ms. Florence Turska
Ms. Stacey Wallick
Mr. Matt Wise
Ms. Li-Yin Xi
Dr. Yantian Zhang
Dr. Ruixia Zhou

Other Federal employees present:
Dr. David Bluemke, Clinical Center, National Institutes of Health
Dr. Kyle Myers, U.S. Food and Drug Administration
Dr. Brad Ward, Clinical Center, National Institutes of Health

Members of the public present for portions of the meeting:
Ms. Renee Cruea, Academy of Radiology Research
Mr. Gareth Hadyk, National Capital Captioning
Ms. Allyson Harkey, NOVA Research Company
Mr. Mike Peters, American College of Radiology
Ms. Kathy Sedgwick, NOVA Research Company
Ms. Sherry Quinn, BearingPoint

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey called to order the 18th 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, Philip Alderson and Cherri Pancake. Dr. Alderson, a longstanding leader in the imaging community, is dean of St. Louis University School of Medicine. He received his training at The Johns Hopkins University and Columbia University, where he was one of the first radiology chairs to forge a strong partnership between imagers and bioengineers. He also testified before Congress regarding the formation of NIBIB.

Dr. Pancake is a professor of electrical engineering and computer science and an Intel Faculty Fellow at Oregon State University. She received her degree in computer engineering from Auburn University. A pioneer in applying ethnographic techniques to identifying software usability problems for the science and business communities, recently Dr. Pancake has focused on how virtual collaborations differ from proximal collaborations. She was instrumental in the creation of the Parallel Tools Consortium and serves as an advisor for various industry, professional, and agency organizations.

B. New Staff

Dr. Pettigrew introduced Guoying Liu, a new Program Director. She comes to NIBIB from NCI, with expertise in imaging, specifically magnetic resonance imaging (MRI).

Dr. Pettigrew also introduced David Bluemke, the new Director of Radiology and Imaging Sciences at the NIH Clinical Center. He has a strong background in the imaging sciences, particularly MRI and computed tomography (CT).

C. Council Member Awards

Dr. Augustus Grant received the American Heart Association's highest national honor, the Gold Heart Award. He has also received the 2008 Duke Alumni Distinguished Faculty Award.

Dr. David Satcher received the inaugural William J. Gies Award for Vision, Innovation, and Achievement from the International Association for Dental Research.

Several NIBIB staff received NIH Director's Awards for outstanding contributions to the mission of the NIH: Zohara Cohen, The NIF Project Team; Valery Gordon, Genome-Wide

Association Studies Policy Development Team; Lori Henderson, Multi-Agency Tissue Engineering Science (MATES); Rosemarie Hunziker, MATES; Christine Kelley, MATES; Mary Beth Kester, NIH Biennial Report Leadership Team; Peter Kirchner, MATES; and Roderic Pettigrew, Outstanding Champions of Peer Review Initiative.

Several NIBIB staff received NIH Blueprint for Neuroscience Research Awards. Individual awards were given to Zohara Cohen for significant contributions in leading the Neuroimaging Informatics Tools and Resources Clearinghouse [NITRC] supplemental funding initiative and James Luo for significant effort in managing the NITRC contract. Team awards were given to the NITRC Project Team (Zohara Cohen, James Luo, and Yantian Zhang) and the Human Embryonic Stem Cell Workshop Planning Team (Rosemarie Hunziker, Lori Henderson, and Christine Kelley).

D. Budget Update

During FY 2008, a supplemental appropriations act added $150 million to NIH's budget; of that, NIBIB received $1.588 million. Consequently, the total NIBIB appropriation for FY 2008 was approximatley $305 million. The FY 2009 NIBIB President's Budget was signed one month prior to the May Council meeting, for $300.3 million.

The final pay plan for FY 2008 is to pay to the 19th percentile for the R01 and R21 mechanisms, except for new investigators who are funded to the 24th percentile. For those mechanisms without percentiles the pay line is a priority score of 165.

E. Significant Activities

New Initiative on Molecular Imaging

The NIH Roadmap was intended to be an incubator space with a maximum 10-year lifespan; at that point, initiatives must sunset, or transition into individual institutes. The first Roadmap initiative supported molecular imaging, with NIBIB as the lead institute. As such, NIBIB has volunteered to move this initiative into NIBIB in FY 2009 as a PAR on "Innovation in Molecular Imaging Probes." The overall goal of the initiative will be to continue supporting projects directed at *in vivo* molecular imaging probes, particularly tackling the problem of increasing sensitivity of molecular imaging probes.

Interagency Modeling and Analysis Group

NIBIB has a strong leadership role in the Interagency Modeling and Analysis Group (IMAG), particularly through Coordinator Dr. Grace Peng. IMAG includes 17 NIH components as well as the National Science Foundation, National Aeronautics and Space Administration, Department of Energy, Department of Defense, U.S. Department of Agriculture, and several corollary European, Japanese, and Canadian agencies focused on multi-scale modeling. IMAG held its third annual meeting in August, in conjunction with the Canadian Society for Industrial and Applied Mathematics.

IMAG's goal is to develop and apply models and analytical methods to biological and biomedical systems across anatomic scales, going from the molecular to whole-organ systems. Work is also ongoing in a broader, longer-range effort ultimately to develop a model of the human physiome—a virtual model of the entire human being, from molecules to the whole organ system.

Indo-U.S. Workshop on Low-Cost Diagnostic and Therapeutic Technologies
In October 2007, NIBIB entered into an agreement with the Indian government to collaborate on developing low-cost diagnostic and therapeutic technologies. The first meeting will be held in November 2008 in Hyderabad, India. The program will focus on major chronic disease areas of interest to both countries. U.S. participants are NIBIB grantees with expertise in technologies that are applicable to the challenges of bringing modern technology to underserved populations, particularly through point-of-care technologies.

Grantee Research
An NIBIB grantee group has developed a $10 microscope. Recently described in the Proceedings of the National Academy of Sciences, the OptoFluidic Microscope (OFM) enables high-resolution (~ 1 micron) on-chip cell and microorganism imaging. Inspired by eye floaters, clumps of microscopic vitreous fibers that are illuminated through an aperture in the eye, the lensless OFM uses very small apertures in combination with microfluidics; the object to be imaged is moved across the apertures. The OFM is approximately the size of a dime, adding to its ease of deployment in the field.

High-Risk, High-Impact Award Program
The High Risk, High Impact Award Program was initiated in FY 2006, with the goal of funding at least two such R01 awards annually. Thus far, five grants have been funded:

- Regulating Stem Cell Growth and Differentiation by Colony Confinement - *Sean Palecek, University of Wisconsin*
- Analysis of Biofilm-Biomaterial Interface - *Luke Hanley, University of Illinois at Chicago*
- Non-Invasive Localization of Vulnerable Plaque - *Cynthia McCollough, Mayo Clinic College of Medicine*
- Minimizing Thrombogenicity of Cardiovascular Implants - *Danny Bluestein, State University of New York - Stony Brook*
- Clinical Multi-Photon, Microscopic Endoscopy - *Watt Webb, Cornell University*

High-Risk, High Impact Award Program grantees will meet in the future with Quantum Program grantees to encourage interaction between the two groups.

HHMI-NIBIB Interfaces Initiative
Begun 3 years ago, the HHMI-NIBIB Interfaces Initiative is a public-private partnership between NIBIB and the Howard Hughes Medical Institute (HHMI), focusing on developing the next generation of research scientists educated in programs specifically crafted to train scientists to think across disciplines. The Initiative comprises two phases: phase 1, supported by HHMI, funded 10 universities over a 3-year period to develop new curricula specifically to train interdisciplinary scientists; in phase 2, NIBIB will fund institutions to implement the curricula. The NIBIB awards will be made in March 2009; applications will be reviewed in January 2009.

F. NIBIB in the News

Steven Lee, a 2007 NIBIB Biomedical Engineering Summer Internship Program (BESIP) intern, received the Ross Award from Purdue University. This annual award is given to one student who exemplifies high academic achievement and overall conduct (leadership, character, etc.).

NIBIB was recently featured in *Diagnostic Imaging.* Dr. Pettigrew was interviewed about the first 5 years of the Institute, its accomplishments, and its future directions.

The work of two NIBIB grantees will be featured on an upcoming *60 Minutes* program. Drs. Jonathan Wolpaw and John Donoghue have been working on the Brain-Computer Interface, a communication pathway between a brain and an external device. Dr. Wolpaw's work has allowed paraplegic individuals to move a small dot on a screen in an intentional direction. The latest version of the technology allows the individual to communicate by spelling words, selecting each letter individually by staring at it.

G. NIH Update—Enhancing Peer Review: Implementation of Recommended Actions

The peer review process overhaul continues to evolve. Some modifications have been made since the last Council update, and NIH is beginning to phase in implementation of selected actions. This phase includes three primary priority areas:

1. *Engage the best reviewers in the peer review system* by increasing flexibility to improve reviewer retention; recruit the best reviewers; improve reviewer training; acknowledge reviewers more formally; and compensate reviewers for their time and effort.
2. *Improve the quality and transparency of the review system* by modifying the rating system to focus on specific criteria; align summary statement with criteria; and shorten and align the application with the rating criteria. This will begin in January 2010.
3. *Ensure balanced and fair review across scientific fields and career stages* by supporting early-stage investigators; review established investigators; enhance review of clinical research; expand awards encouraging transformative research; and reduce need for resubmissions.

NIH is considering separate percentiling of new and resubmitted applications and allowing only one amended application. NIH will establish an early-stage investigator designation to distinguish new investigators from those who are merely new to NIH.

Over the last decade, the likelihood of being funded on the first submission has plummeted, which keeps applications in the review process for an extended period of time, clogging the system and delaying research. NIH hopes that allowing only one amended application will increase researchers' opportunities to succeed on the first application.

Discussion

Council members expressed concern that the changes could increase the number of applications. Dr. Pettigrew indicated that the change to shorter applications, for example, is primarily intended to improve the correlation between the score and the merit of the grant by having more reviewers review the application, which can be achieved more easily with a shorter application. Dr. Seto indicated that the NIH will monitor both the number of applications submitted and study section reviewer behavior.

H. Council Regulations, Policies, and Procedures

Dr. Demsey noted that a quorum was present for this Council meeting. Dr. Judy Raper is no longer with the National Science Foundation and, thus, is no longer the NIH ex officio member

of the Council. She has been replaced by Dr. John McGrath, formerly of the Arizona State University. Dr. McGrath was unable to attend today; Dr. Sohi Rastegar is representing him.

Dr. Demsey welcomed visitors and members of the science press and scientific society constituencies. He also thanked Ms. Carol Fitzpatrick and Ms. Pam Glikman for planning the meeting and especially for their work on the first fully electronic mail-outs to Council members.

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 U.S. Department of Health and Human Services 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 guidelines regarding conflict of interest, confidentiality, and lobbying.

I. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for January 23, 2009, at the Bethesda Marriott Suites in Bethesda, Maryland. Dr. Demsey asked Council members to inform him of major conflicts with upcoming meeting dates. The meeting dates are also available via the electronic Council book.

J. Approval of the May 16, 2008, NACBIB Meeting Minutes

A motion was made and seconded to approve the minutes of the May 16, 2008, NACBIB. The minutes were approved unanimously with no corrections.

Dr. Demsey reminded the Council that all meeting agendas and minutes are available on the Council Web site.

III. Molecular Imaging Program at the NIBIB: Dr. Yantian Zhang

Dr. Yantian Zhang provided an update on NIBIB's Molecular Imaging Program (MIP), which supports the development, evaluation, and application of molecular imaging agents as well as imaging methodology development to study normal and pathophysiological processes at the cell and molecular level. MIP's research portfolio includes approximately 90 grants and total funding of approximately $21 million per year. Grants cover a wide range of imaging modalities—optical, magnetic resonance, ultrasound, nuclear, computed tomography, and combinations thereof—at basic, pre-clinical, clinical, and training developmental stages.

Top experts in the field attended MIP's progress review meeting in May to help NIBIB take stock of the program and to provide input for future research directions. Preliminary recommendations include the following:

- *Encourage work on promising new targets*.
- *Target/probe normal cells* to study biochemical anatomy of the cells of the body, microRNAs, siRNAs, etc.
- *Focus on translation and overcome barriers* such as delivery and pharmacokinetics, signal strength, identification of specific activity, and validation of biomarkers.
- *Focus on chemistry and encourage quantitation*.

Imaging Agent and Molecular Probes Development Grants
Several MIP grantees are working with contrast agents to improve sensitivity to small changes and specificity about the target.

Gold Nanorods as Optical Contrast Agents—Alex Wei, Purdue University
Gold nano-particles are widely used as contrast agents in optical imaging research because they are bright, nontoxic, and provide desirable therapeutic effects in hyperthermia treatment. Dr. Alex Wei uses nanorods whose absorption profile is directly proportional to the nanorod's length to diameter aspect ratio. These nanorods can be made to absorb in the near-infrared spectral region, which presents a window of opportunity for optical imaging due to reduced tissue light absorption in the near IR region. Used with two photon microscopy, images of a mouse model using gold nano-rods as the tracer exhibited almost no competing background noise. This example demonstrated improved sensitivity and specificity.

OCT Contrast Agents for Molecular Imaging—Stephen Boppart, University of Illinois at Urbana-Champaign
Dr. Stephen Boppart has been developing optical coherence tomography (OCT) contrast agents to deal with penetration depth and specificity/selectivity challenges. He has developed four classes of agents: scattering agents that potentially are more medically specific; magnetic agents; spectroscopic agents; and plasmon-resonant agents.

Off Resonance MRI—Jinming Gao, University of Texas Southwestern Medical Center
Dr. Jinming Gao has been developing superparamagnetic polymeric micelles as sensitive molecular imaging probes. Instead of using the common T2* contrast effect of superparamagnetic particles, Dr. Gao uses the superparamagnetic particles' property of line broadening to turn the contrast effect on and off through off-resonance saturation by MRI. This represents a big step forward toward achieving greater specificity through the reduction of competing background noise.

Imaging of LRP-Transfected Glioma Cells—Jeff Bulte, The Johns Hopkins University
Dr. Jeff Bulte is developing in vivo cell labeling for the purpose of cell tracking and other molecular imaging applications. Using the so-called CEST (chemical exchange saturation transfer) effect, LRP (Lysine Rich Protein)-transfected glioma cells produced MRI signal contrast not observable from control cells similarly transfected but with EGFP reporter gene. In addition to cancer cells, stem cells can also be labeled for various research applications.

Nuclear Medicine and Optical Imaging Agent Grants
Dr. Zhang listed MIP-supported research in nuclear medicine and optical imaging: new imaging agents for studying gene expression; VEGF-driven PET imaging of tumor angiogenesis; imaging apoptosis *in vivo* with technetium 99m annexin; and a PSMA-based gene reporter-probe system.

Potential Future Directions for Imaging Agent Development
After a very brief review of the history of imaging agent development, Dr. Zhang further discussed general future directions for this field of research, in pursuit of improved imaging sensitivity and specificity. One particular possibility presented was the development of more "active" imaging/therapy agents such as those that actively perturb targeted biological and pathophysiological processes. The active perturbation could potentially lead to specific responses from the imaging/therapy targets, which in turn could be further exploited for improving imaging/therapy sensitivity and specificity.

Imaging Methodology Development Grants
The MIP also supports researchers working on molecular imaging methodology development, such as:

Molecular Imaging: Optical Technology—Vasilis Ntziachristos, Massachusetts General Hospital and Ge Wang, Virginia Polytechnic Institute and State University
The work of Dr. Wang and of Dr. Ntziachristos in fluorescence/bioluminescence tomography aims to accomplish tomographic image reconstruction by modeling photon transport in tissue.

Photoacoustic Microscopy—Lihong Wang, Washington University in St. Louis
The uniqueness of Dr. Lihong Wang's work lies in its combined use of light and ultrasound to create images—sending one form of energy to the target for excitation and creating images using resultant emission from another form of energy. Images formed from ultrasound sidestep the depth penetration limitation of common optical imaging.

OptoFluidic Microscope—Changhuei Yang, California Institute of Technology
The OptoFluidic Microscope (previously mentioned by Dr. Pettigrew) was developed with NIBIB funding. This lensless microscope consists of microfluidic channels and CCD detectors. It can be easily fabricated at very low manufacturing cost and can achieve the performance of conventional microscopes. Its adaptability for point-of-care use offers clear advantages over conventional microscopes.

Discussion
A Council member expressed surprise at the high percentage (25%) of the portfolio spent on MR versus the low percentage (12%) on PET/SPECT. Dr. Zhang responded that different criteria could affect categorization; for example, categorization criteria for the PET/nuclear medicine portfolio depend on the proportion of work directed at that specific modality. In addition, the percent of portfolio in various image modalities would not be truly reflective of the makeup of these modalities in the actual molecular imaging field, given the limited number of grants supported by MIP.

Another member asked whether researchers in this field have attempted to image viruses. Dr. Zhang responded that none of the work supported by the NIBIB has done so directly, but many optical and molecular imaging techniques could potentially be used for this purpose. Dr. Pettigrew described Roadmap initiative-supported research at Harvard University where investigators have used fluorescent probes to look at the relationship between the virus and adjacent structures required for the virus to gain entry into the cell.

Another member asked Dr. Zhang to comment on the degree to which current research could be classified as translational. Dr. Zhang stated that the program would like to support more translational research; for example, Dr. Bulte's project and some of the other MR grants use MRI technology, which is an imaging modality used in the clinic. Such research can lead to clinical translation.

Finally, another Council member asked how recommendations from the progress review meeting (e.g., focusing on new targets) will be implemented. Dr. Zhang responded that MIP planning would produce initiatives focused on the recommendations, and a PAR touching on the recommendations will be issued as part of the transition from the Roadmap to NIBIB.

IV. Prostate-Specific Membrane Antigen (PSMA): A Versatile Target for Molecular Imaging: Dr. Martin Pomper

Dr. Alan McLaughlin, director of NIBIB's Division of Applied Science and Technology, introduced Dr. Martin Pomper. Dr. Pomper earned his M.D. and Ph.D. from the University of Illinois and completed postgraduate training at The Johns Hopkins University. He is currently an associate professor of neuroradiology, director of the Small Animal Imaging Resource Program, and deputy director of the *In vivo* Cellular and Molecular Imaging Center at Johns Hopkins. Dr. Pomper is a member of the Johns Hopkins Vasculitis Center and the New Approaches to Brain Tumor Therapy consortium. Dr. Pomper's research in central nervous system imaging employs MR spectroscopy and PET to study abnormalities in patients with AIDS dementia and design of new radiopharmaceuticals for imaging neurotransmitters. He is also interested in new approaches to imaging prostate cancer.

Dr. Pomper traced the evolution of diagnostic imaging from purely anatomic techniques (e.g., CT, MR, and ultrasound), functional techniques (e.g., profusion MR and CT), radiopharmaceutical-based techniques, and hybrid techniques (e.g., PET/CT, SPECT/CT, PET/MR) to molecular imaging modalities (e.g., nuclear medicine, PET, SPECT, MRS, optical, PET/MRI, and contrast-enhanced MRI/US/CT). Molecular imaging enables noninvasive assessment of cellular and other metabolic processes *in vivo* and under physiologic or pathologic conditions.

Molecular imaging allows early detection of physiologic changes in tumor tissue and thereby enables monitoring individual patient response to therapy in real time (personalized medicine). Various molecular imaging modalities differ in their abilities to translate from preclinical to human studies and offer different sensitivities for detecting molecular phenomena. Dr. Pomper's lab focuses on radiopharmaceutical-based techniques, which he believes have the best combination of high sensitivity and translatability. Thanks to their high sensitivity, radiopharmaceutical techniques are translatable to the clinic because only small doses of the toxic tracers are required for imaging.

Prostate-specific membrane antigen (PSMA) is an enzyme in the prostate, brain, and other tissues that cleaves acetyl aspartate glutamate to produce glutamate and acetyl-aspartate. One of Dr. Pomper's current projects is designing substrate-type and receptor-type probes for PSMA that could be used in high-sensitivity molecular imaging. The project's main goal is to generate multimodality PSMA-based imaging agents for cancer imaging and therapy. PSMA is a good candidate for cancer imaging and therapy because it has high sensitivity; it is non-immunogenic in humans, expressed in many tissues, and present in high numbers on the cell surface. Dr. Pomper's team developed low-molecular-weight probes for PSMA that are hydrophilic, so they do not bind non-specifically to other tissues. Some probes can be internalized by cells, which provides another amplification mechanism.

These compounds can be used to image prostate cancer or other cancers because PSMA is overexpressed in vessels of many tumors. Prostate cancer recurrence is particularly difficult to pinpoint in post-prostatectomy patients; in order to deliver the right kind of therapy, a clinician needs to image the cancer. Currently, prostasin, a monoclonal, radio-labeled antibody that binds to PSMA, is used as an imaging agent for prostate cancer. However, antibodies do not make particularly good imaging agents because they tend to be large and have a long blood-pool phase.

In contrast, low molecular weight PSMA probes have a short blood-pool phase, contributing to their high sensitivity.

Dr. Pomper's carbon-11-labeled PSMA probe produced a 10-to-1 target-to-background ratio as opposed to prostasin's 2-to-1 or 3-to-1 target-to-background ratio. However, carbon-11's 20-minute half-life is too short for clinical use. In contrast, fluorine-18 radiotracer's 2-hour half-life is more compatible with clinical use. Dr. Pomper was able to obtain semi-quantitative imaging data using one injection of the fluorine-18 radiotracer in transgenic mice bearing prostate tumors with PSMA. This compound is now undergoing toxicity studies. Dr. Pomper hopes to begin patient studies within the next 2 months. Some of his most recent PSMA radiotracers display target-to-background ratios up to 40-to-1.

Technetium has the best imaging characteristics of any radionuclide, but because it is a metal, it requires a linker to hook it to the target molecule. Sangeeta Ray, a research associate in the Pomper lab, has developed a single amino acid chelate concept, that allows binding of technetium with amino acids, such as the PSMA glutamate probe. Technetium-based probes yield a 50-to-1 target-to-background ratio and can be used both for diagnostic or therapeutic purposes. In addition, probes designed to be both radioactive and fluorescent offer a way to look at PSMA optically and follow its kinetics *in vivo*. Dr. Pomper has patented this technology and licensed it through *Molecular Insight Pharmaceuticals*. The company has also created derivatives of some of the compounds and obtained the first images of a patient with prostate cancer, detecting a periaortic node metastasis not detectable on a CT scan.

Dr. Pomper is also working with Jefferson National Labs to develop a prostate-only PET scanner, to further increase sensitivity of the technique. His group is developing near-infrared probes based on the PSMA-binding compounds for intraoperative guidance during resection to ensure that there is no more tumor within the operative bed.

PSMA has been shown to be dysregulated in schizophrenia and appears to be an attractive target for diagnostics in psychiatry. Dr. Pomper's team found that radioactive prostate agents bind specifically to PSMA in the brain. In post-mortem analyses, Dr. Pomper could detect differences in PSMA levels in the brains from schizophrenic patients compared to brains from normal individuals. Furthermore, by looking at specific brain regions, PSMA probes can be used to distinguish schizophrenic patients from those with bipolar disorder. Dr. Pomper's next goal is to modify these compounds so that they can penetrate the blood-brain barrier and be used as an *in vivo* imaging agent to study brain disorders.

A number of cancers (e.g., lymphoma, Kaposi's sarcoma, nasal pharyngeal carcinoma, gastric cancer) carry dormant Epstein-Barr viruses (EBV). Dr. Pomper has been collaborating with Richard Ambinder (Johns Hopkins), who is interested in using pharmacologic agents to treat cancer by activating the virus inside the body. When activated, the virus starts to reproduce and kills its host cancer cell in the process. However, these agents are somewhat toxic and work in approximately 20% of patients with EBV-tumors. Dr. Ambinder has partnered with Dr. Pomper in an effort to use molecular imaging of patients' tumors to determine whether EBV becomes activated in response to the pharmacological agents. When EBV is awakened, the virus turns on a gene called EBV thymidine kinase, which Ambinder and Pomper used as a reporter gene to determine the activation status of the virus *in vivo*. After receiving a pharmacological agent to wake up the virus, a patient would receive a specific probe (FIAU) for EBV thymidine kinase

and, if the virus were activated, the tumor would light up. If the tumor doesn't light up, doctors can immediately move to a different therapy. This imaging approach has been validated in mice, and studies in humans will begin soon. In addition, by changing the radionuclide on the FIAU probe to iodine-131, the same imaging agent can be used as a tumor-killing therapy for various cancers, including lymphoma and gastric carcinoma. The treatment is noninvasive, as the target protein—thymidine kinase—is already in the tumor cells infected by EBV.

Initial outcomes of Dr. Pomper's grant include seven publications and three patent applications; synthesis of approximately 100 new ligands and substrates; a high-sensitivity, site-directed imaging agent in clinical trials; an NIH Ruth L. Kirschstein fellowship for graduate student Mark Castanares; and new collaborations with NCI-Frederick (Jacek Lubkowski) and Duke University (Michael Zalutsky) and deeper interaction with Jefferson National Laboratories, Johns Hopkins Urology, and the Johns Hopkins Institute for Cell Engineering.

Dr. Pomper thanked Dr. Pettigrew, NIBIB, the Roadmap Initiative, NCI Cancer Imaging Program, Department of Defense, AdMeTech Foundation, and Patrick C. Walsh Foundation for their support.

Discussion

Dr. Seto asked about the correlation of enzymatic activity of PSMA to the metabolic state of prostate cancer cells. Dr. Pomper responded that PSMA is expressed in androgen-independent disease and particularly in stages that are more malignant. Thus, one can draw conclusions about the state of the tumor based on PSMA activity.

Dr. Pettigrew asked about the X-ray crystallography and modeling used to design his probes for PSMA. Based on the crystal structure data, computational docking studies are conducted to design various compounds that fit in the protein's active site, and the most promising probe candidates are synthesized. Dr. Cyril Barinka at NCI-Frederick co-crystalized PSMA with the various new probes to verify that the probes truly bind to PSMA, as predicted by computer models.

V. Optical Molecular Imaging Applications: Dr. Umar Mahmood

Dr. McLaughlin introduced Dr. Umar Mahmood, associate professor of Radiology at Harvard University and director of the Mouse Imaging Program at the Center for Molecular Imaging Research. Dr. Mahmood earned his Ph.D. and M.D. from Cornell University and completed his postgraduate work at Memorial Sloan-Kettering Cancer Center. His research interests focus on designing optical, MRI, SPECT, and CT instrumentation for small animal imaging and optimization of molecular imaging of specific disease models.

Dr. Mahmood presented an overview of molecular imaging as a multidisciplinary field that integrates research on devices, probe chemistry, and the biology of targets. Molecular imaging can enable early disease detection, patient stratification according to the degree of target overexpression, individualized dosing of molecularly specific therapy, earlier therapeutic response evaluation, and easier evaluation of combination therapy.

Unlike MRI or PET devices, optical devices are application-specific. Optical imaging can be quantitative, allows imaging on different scales (from whole organ to cellular level), and tends to be relatively inexpensive compared with other modalities. Optical systems also can be made to

view multiple targets at the same time, which is very valuable as most diseases are associated with more than one abnormality.

Each modality has its strengths and weaknesses. MRI has high spatial resolution and great intrinsic contrast but tends to have low sensitivity for evaluating molecular targets. PET has high sensitivity, but it has low spatial resolution and uses radioactivity. Ultrasound is useful for intervention but is not as useful for quantitation, while CT has high resolution but gives little molecular information. Bioluminescence and fluorescence protein imaging are preclinical and not translatable because they require introduction of foreign genes and are associated with low depth penetration. Fluorescence optical imaging (i.e., tomographic imaging and minimally invasive endoscopic imaging) uses smart agents that change properties, allows one to look at multiple targets, and has high sensitivity; however, some body parts are not accessible.

With respect to chemistry, fluorochromes often last longer than radioisotopes, allowing one to image at later time points. On the downside, fluorochromes tend to be bigger than radioisotopes, so that fluorochrome labeling of small molecules can change their biodistribution or pharmacokinetics. Distribution of larger molecules (e.g., peptides, antibodies, macromolecules) is less affected by fluorochrome labeling.

One of Dr. Mahmood's projects involves imaging proteases as biomarkers of tumor state. This type of imaging provides information on the specific location of the abnormality. Increased expression of numerous proteases is associated with tumor progression, increased metastasis formation, and increased angiogenesis. Different protease enzymes can be imaged using specific probes. The protease probes are designed to light up when they interact with a protease molecule.

Dr. Mahmood presented several potential clinical applications of fluorescence optical imaging. For example, imaging protease activity in pre-cancerous growth could show a colonoscopist where to sample. Dr. Mahmood and his colleagues have developed a submillimeter mouse endoscopy setup, with 10,000 imaging fibers. White light is applied to provide all the hues an endoscopist uses to obtain anatomic information. In addition, the light is split to acquire molecular information in the near-infrared spectrum. Recently, Dr. Mahmood has developed ways to quantitate the fluorescent signal in this minimally invasive approach.

Dr. Mahmood has also used optical imaging in cardiovascular disease. Possibly, the protease is overexpressed within the fibrous cap and potentially makes plaques more vulnerable; using a protease probe, one could potentially identify plaques that are more likely to rupture. Certain proteases are related to aneurysm growth. Protease probes might be used to predict which abdominal aortic aneurysms are likely to grow and therefore require intervention.

A number of different biological colon cancer models exist, including APC Min and AOM. Dr. Mahmood and his colleagues employ many different models to evaluate their probes. They have developed a focal mucosal disruption method, wherein they implant the tumor from the mucosal surface. Dr. Mahmood's group teamed with Dr. Roger Rajulapati, a mouse model developer, to generate tumors of known age and location. With Dr. Mahmood’s probes, the fluorescence signal remains essentially unchanged whether close up or far away; this allows for increased specificity. For example, using the probes in *ex vivo* studies, the tumor to mucosa luminosity ratio increased from 1-to-1 to 9-to-1.

Because optical imaging is conducted in real time, it is useful as a sampling guide. For example, during laparoscopy, a physician can use fluorescence probes combined with devices to ensure that the right sites are sampled and to look for residual disease in an intraoperative setting, or in a minimally invasive fashion. Dr. Mahmood has applied the same approach to imaging lung cancer (9-to-1 target-to-background ratio), esophageal adenocarcinoma (5-to-1), transitional cell carcinoma in the bladder (4-to-1), and ovarian cancer (5-to-1 to 8-to-1).

Peptide-based fluorescent probes can also be used to image tumors *in vivo*. Working with Dr. Kim Kelly, Dr. Mahmood has developed fluorescent peptides that recognize targets in pancreatic and colon cancer. This approach is translatable for both optical imaging and for radio-imaging. He also designed fluorescent Herceptin, a breast cancer drug that targets the Her-2 protein. Using this probe, doctors could readily see which patients have Her-2 in their tumors and are therefore likely to respond to Herceptin therapy.

Optical imaging allows examination of multiple targets, which is difficult in other modalities. In optical imaging, wavelengths can be separated easily using appropriate filters at high target-to-background ratios (50- to 100-to-1), so that different gene expressions can be viewed simultaneously. For example, when trying to define disease, one can look at several targets to determine which genes will cause a tumor to spread. One can perform spectral deconvolution to separate signals from different fluorochromes or spread the spectrum into a second dimension based on different rates of decay for different fluorochromes. These improvements will potentially allow simultaneous imaging of up to 15 targets. Recently, Dr. Mahmood has been examining ways to apply optical imaging to look at different gene abnormalities; for example, using a confocal catheter to look at the size and complexity of blood vessels, he hopes to characterize treatment responses in pancreatic tumors with different genetic profiles.

Dr. Mahmood is also developing multimodal probes. For example, iron-oxide nanoparticles, which are used in MR, can be fluorescently labeled for optical imaging. Such probes might be used to label white blood cells *ex vivo* and then track their movement through the body in basic biology research, as well as in the clinic (e.g., during preoperative or prebiopsy MR scans). A surgeon could use this approach to determine resection margins.

Optical imaging can be used to evaluate the mechanisms of new drugs. One of Dr. Mahmood's collaborators, Dr. Lee Josephson, invented a compound that could be used for prevention and treatment of rheumatoid arthritis. Dr. Mahmood's team used optical imaging to determine how this new drug works on a molecular level (i.e., they looked at proteases in the joints, vascular leaks, and immune system responses).

Optical imaging has a number of strengths. Imaging of molecular activity potentially allows earlier detection of disease and characterization of lesions *in situ*. Fluorescent probes can be activated, are stable, and have high spatial relation. The potential for imaging multiple targets simultaneously may increase the sensitivity and specificity of disease evaluation. Importantly, human translation is possible across a diverse array of diseases.

Dr. Mahmood thanked NIH and NIBIB for his grant support.

VI. Adjournment

The open session of the NACBIB meeting was adjourned at 12:25 p.m.

VII. Closed Session

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

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 January 23, 2009, and corrections or notations will be stated in the minutes of that meeting.