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 20, 2012

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 28th meeting on January 20, 2012, 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 12:00 noon for review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:00 p.m. to 1:45 p.m. for consideration of individual grant applications.

Council members present:
Dr. Philip Alderson, Saint Louis University, St. Louis, MO
Dr. John C. Gore, Vanderbilt University, Nashville, TN
Dr. Nola M. Hylton, University of California, San Francisco, CA
Dr. Cato T. Laurencin, The University of Connecticut, Farmington, CT
Dr. Mark Musen, Stanford University, Stanford, CA
Dr. Etta D. Pisano, Medical University of South Carolina, Charleston, SC
Dr. Buddy Ratner, University of Washington, Seattle, WA
Dr. Michael Yaszemski, Mayo Clinic College of Medicine, Rochester, MN

Ex officio members present:
Dr. Anne Plant, National Institute of Standards and Technology, Gaithersburg, MD
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences, Bethesda, MD

Council member present via conference call:
Dr. Cherri Pancake, Oregon State University, Corvallis, OR

Ad hoc Council member present via conference call:
Dr. Gary Glover, Stanford University, Stanford, CA

Ex officio Council member present via conference call:
Dr. P. Hunter Peckham, U.S. Department of Veterans Affairs, Cleveland, OH

Council members absent:
Dr. W. Eric L. Grimson, Massachusetts Institute of Technology, Cambridge, MA
Dr. Hedvig Hricak, Memorial Sloan-Kettering Cancer Center, New York, NY

Ex officio members absent:
Dr. Francis Collins, National Institutes of Health, Bethesda, MD
Dr. John McGrath, National Science Foundation, Arlington, VA
Ms. Kathleen Sebelius, U.S. Department of Health and Human Services, Washington, DC

[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 occur. This procedure only applies to applications that are discussed individually, not to "en bloc" actions.

Chairperson:
Dr. Roderic I. Pettigrew

Executive Secretary:
Dr. Anthony Demsey

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

Mr. Angelos Bacas
Dr. Richard A. Baird
Ms. Sheila Barrett
Ms. Michelle Byrd
Ms. Barbara Cantilena
Ms. Patty Clements
Ms. Shirley Coney-Johnson
Dr. Richard Conroy
Ms. Stephanie Cooperstein
Ms. Zoe-Ann Copeland
Ms. Marilyn Daly
Ms. Monique Day
Mr. Jeff Domanski
Dr. Henry Eden
Ms. Angela Eldridge
Ms. Kathryn Ellis
Dr. Zeynep Erim
Ms. Carol Fitzpatrick
Dr. David George
Ms. Marie Gill
Ms. Pam Glikman
Dr. Valery Gordon
Dr. Ruth Grossman
Dr. John Hayes
Ms. Eunica Haynes
Dr. William Heetderks
Mr. James Huff
Dr. Rosemarie Hunziker
Mr. Tom Izzard
Dr. Thomas Johnson
Mr. Jeff Kaloz
Ms. Kai Kamerow
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Peter Kirchner
Dr. Brenda Korte
Dr. Steven Krosnick
Dr. Richard Leapman
Mr. Eugene Lee
Dr. Christina Liu
Dr. Guoying Liu
Dr. Hector Lopez
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Larry Morton
Mr. Joe Mosimann
Dr. Vinay Pai
Dr. Grace Peng
Dr. Karen Peterson
Ms. Vicki Rein
Ms. Christine Rogers
Ms. Nicole Rohloff
Mr. Rolando Romero
Ms. Stephanie Sabourin
Dr. Antonio Sastre
Dr. Belinda P. Seto
Mr. Shaun Sims
Dr. Manana Sukhareva
Ms. Desi Tubb
Ms. Florence Turska
Ms. Keisha Whitaker-Duncan
Mr. Kwesi Wright
Dr. Ruixia Zhou
Dr. Steven Zullo

Non-NIBIB NIH employees:
None

Non-NIH Federal employees:
None

Members of the public present for portions of the meeting:
Ms. Renee Cruea, Academy of Radiology Research
Mr. Sean Gallagher, American Institute for Medical and Biological Engineering
Ms. JoAnne Goodnight, ITECS Innovative Consulting Technology Marketing Development
Ms. Allyson Harkey, NOVA Research Company
Mr. Vhic Mata, Event Technology Solutions
Mr. Stephen Murphy, IQ Solutions
Ms. Virginia Neale, Lewis-Burke Associates
Dr. Sarah J. Nelson, University of California, San Francisco
Mr. Michael Peters, American College of Radiology
Mr. Kevin Salinas, Event Technology Solutions
Mr. Matt Sherman, National Capital Captioning
Mr. JJ Smith, *Government Video Magazine*
Mr. Rick Tamayo, Event Technology Solutions

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey called to order the 28th meeting of the National Advisory Council for Biomedical Imaging and Bioengineering. He reminded attendees that the morning session of the meeting was open to the public, welcomed attendees, and introduced Dr. Pettigrew, who formally welcomed all participants.

II. Director's Remarks: Dr. Roderic I. Pettigrew

A. NIBIB Achievements

Two NIBIB grantees were awarded Presidential Early Career Awards for Scientists and Engineers, the highest honor bestowed upon an early-stage investigator by the Federal Government. Drs. Brian Caffo (The Johns Hopkins University) and Carla Pugh (Northwestern University) were among the 90 researchers who received awards. Dr. Hari Shroff, Chief of NIBIB's High Resolution Optical Imaging Section, was also recognized for his development of a technology that exceeds the theoretical resolution limit imposed by light diffraction.

Dr. Guoying Liu, Program Director of the Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) programs at NIBIB, has been elected to the American Institute of Medical and Biological Engineering 2012 College of Fellows, which represents the top 2 percent of engineers in the country who work in medical and biological fields. Dr. Liu was recognized for her contributions to the development and clinical application of magnetic resonance imaging techniques.

Dr. James Smirniotopoulos, ex officio Council member, was named the 2011 Radiological Society of North America Outstanding Educator. Only one person receives this award each year. Dr. Smirniotopoulos was recognized for his longstanding career, legacy of innovation in radiation and pathology, and unique lecture style.

B. Budget and Legislation

President Obama signed the National Institutes of Health (NIH) Fiscal Year (FY) 2012 budget on December 23, 2011. The budget contains several special stipulations, including the creation of the National Center for Advancing Translational Sciences (NCATS). Dr. Thomas Insel will serve as Acting Director, and Dr. Kathy Hudson will serve as Acting Deputy Director. NCATS staff largely comes from the former National Center for Research Resources (NCRR), which was dissolved.

The NCRR portfolio has been divided among NCATS, the NIH Office of the Director, the National Institute of General Medical Sciences, the National Institute on Minority Health and Health Disparities, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Heart, Lung, and Blood Institute, and NIBIB. NIBIB will receive $24 million for approximately 50 transferred grants, and three personnel positions will be shifted to NIBIB as well.

The NIBIB budget appropriation for FY2012 is $338 million, including the transfers from NCRR. This represents a 0.4 percent increase from the FY 2011 budget of $314 million. Without the transferred funds from NCRR, the 2012 budget is essentially flat.

The phenomenon of increased numbers of R01 applications within a given percentile, first observed in January 2010, has continued through the January 2012 round. January 2012 shows a 60-percent increase in the number of applications scoring within the 10th percentile over January 2009; this increase is less than in January 2010 and January 2011 but is still significant. The 2012 payline will be approximately the 10th percentile, down from the 11th percentile in 2011.

The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs were reauthorized for six years as of December 31, 2011. Several significant changes have been made to the programs. Over the next six years, the congressionally mandated set-aside for SBIR will increase incrementally from 2.5 percent to 3.2 percent; the set-aside for STTR will increase from 0.30 percent to 0.45 percent. The Phase I guideline for STTR awards has been increased to $150,000. New hard limits for both SBIR and STTR awards are set at $225,000 (Phase I) and $1.5 million (Phase II). Venture capital firm participation has been expanded; the SBIR/STTR programs can now award up to 25 percent of their funds to small businesses with venture majority ownership. Finally, technical assistance programs have been increased to $5,000 per year per Phase I and Phase II award.

C. Design by Biomedical Undergraduate Teams (DEBUT) Challenge

The America COMPETES Act, signed one year ago, gives Federal agencies authority to issue competitive prizes intended to spur technological innovation and development. NIBIB's Design by Biomedical Undergraduate Teams (DEBUT) Challenge will award $10,000 to undergraduate, team-based design projects in three categories: diagnostic devices/methods, therapeutic devices/methods, and technology to aid underserved populations and individuals with disabilities. Winners will also receive up to $2,000 in travel and registration funding to attend the NIBIB DEBUT Award Ceremony in conjunction with the Biomedical Engineering Society Annual Meeting in October 2012. The entry deadline is May 26, 2012; winners will be announced July 31, 2012.

D. Indo-U.S. Summit

The Advances in Health Care Through Accessible Technologies: A U.S.-Indo Grand Challenge meeting held in December 2011 brought together individuals from academia, industry, and government to discuss and identify major health care problems common to both countries that can be addressed by affordable, accessible technological innovation. The basic concept of the meeting was to identify a key problem and develop an initiative to solve the problem. The meeting was held in conjunction with the Indian Medtech Summit, sponsored jointly by Stanford University and India.

Meeting participants considered three major health areas on which affordable, accessible technological innovation could make an impact, and developed two leading opportunities to help redress large-scale health problems globally for each of these areas: hypertension (acquire high-

quality blood pressure data passively over time; monitor lifestyle activities and provide compelling coaching advice); diabetes (a. accurate screening, diagnosis, and monitoring non-invasively, in ambient conditions; b. technology-delivered education of patients on diagnosis and management of complications); and cancer diagnostics (a. screening and early detection of common, treatable cancers such as cervix and oral; b. preparation, preservation, and analysis of non-invasive peripheral samples or biofluids to detect cancer biomarkers). Participants chose hypertension, diabetes (topic a), and cancer diagnostics (topic a) as the most compelling opportunities.

Following further discussion, NIBIB leadership has concluded that hypertension, as a key problem, represents the greatest opportunity. A leading risk factor for death across the globe, the level of hypertension correlates with the level by which one's life expectancy is reduced; that is, a mild increase in blood pressure results in a mild decrease in life expectancy and a greater increase in blood pressure results in a greater decrease in life expectancy. Hypertension is often undetected and, when detected, difficult to manage; however, it is treatable. Low-cost technologies could improve the ability to manage this problem globally. Ideally, teams comprising researchers from both the United States and India will develop technologies to monitor a person's blood pressure unobtrusively and continuously, and provide data in feedback form to both physician and patient.

E. NIBIB 10th Anniversary

NIBIB's 10th anniversary will be celebrated June 21-22, 2012, with a dinner and a scientific symposium. Confirmed speakers include NBC News Chief Health and Science Correspondent Robert Bazell, NIH Director Dr. Francis Collins, General Electric Chief Executive Officer Jeff Immelt, National Academy of Engineering President Dr. Charles Vest, Nobel Laureate and Massachusetts Institute of Technology (MIT) Professor Dr. Phillip Sharp, and Nobel Laureate and University of California, San Diego, Professor Dr. Roger Tsien.

F. Research in the News

Dr. Paula Hammond and her research team at MIT are addressing the problem of treating tumors, which are characterized typically by a hypoxic and acidic environment. Because of this environment, delivery of agents to tumors is challenging. Hypoxia also results in radiation and chemotherapy resistance. Dr. Hammond's solution concept is to develop a multifunctional nanoparticle with a variety of layers. An outer ("stealth") layer hides the next layer's positive charge; the stealth layer is shed when it encounters the characteristically acidic tumor environment. The second layer's positive charge induces particle uptake by tumor cells, and inner layers with multiple drugs to lower tumor defense mechanisms and chemotherapy to kill tumor cells are revealed. The first *in vivo* demonstrations of this concept in a mouse model showed positive effectiveness in exploiting the tumor microenvironment.

Dr. Sam Stupp and his research team at Northwestern University have developed an angiogenic nanostructure to promote ischemic tissue repair. With a hydrophobic tail and a hydrophilic head, the molecule when injected into a fluid assembles into a nanofiber that has a high-density head. In Dr. Stupp's work, the nanofiber—called an *amphiphile*—contains vascular endothelial growth factor (VEGF) on its head. In an ischemic chicken model, using the VEGF amphiphile increased vascular regrowth about 200 percent.

Georgia Institute of Technology's Dr. Maysam Ghovanloo has developed a tongue-based assistive neurotechnology for individuals with severe neurological disorders. This research was funded by an NIBIB American Recovery and Reinvestment Act Challenge Grant. The neurotechnology allows quadriplegics to manipulate wheelchairs, interact with computers, play video games, use a

cell phone, etc., using a wireless tongue drive. A small permanent magnet attached to the user's tongue interacts with an array of magnetic sensors mounted on a custom-designed headset to detect a change of magnetic field as a result of tongue movement. A control unit collects sensor outputs and then wirelessly transmits them to a smartphone, which then translates sensor outputs into control commands to operate different devices in the user's environment, such as a wheelchair or a computer.

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

Dr. Demsey noted for the record that a quorum was present for this Council meeting. Council members Drs. Hedvig Hricak and Eric Grimson were unable to attend; Drs. Cherry Pancake and Gary Glover will join the closed session via telephone. Dr. Demsey welcomed visitors and members of the science press and scientific society constituencies. He thanked Ms. Carol Fitzpatrick and Ms. Pam Glikman for planning the meeting.

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 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, NACBIB meetings are open to the public for all except the review of individual grant applications. Dr. Demsey reviewed conflict-of-interest, confidentiality, and lobbying guidelines.

The Council Operating Procedures have been updated. The only minor change is on page 5 in the last sentence before "B. Council Discussion Items": *applications unscored* has been changed to *applications that were not discussed.* A motion to approve the updated Operating Procedures was forwarded, seconded, and unanimously approved.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for Monday, May 21, 2012, with the site to be determined. Dr. Demsey asked Council members to inform him about conflicts with any of the upcoming meeting dates listed at the bottom of the agenda.

C. Approval of the September 12, 2011, NACBIB Meeting Minutes

A motion to approve minutes of the September 12, 2011, NACBIB meeting was forwarded, seconded, and approved unanimously.

IV. Introduction to Hyperpolarized ^{13}C MRI: Guoying Liu, Ph.D.

Dr. Guoying Liu presented an overview of hyperpolarized carbon-13 (^{13}C) MRI and its use for metabolic imaging *in vivo.* Dr. Liu received her Ph.D. in physical chemistry in 1991 from the University of Illinois at Urbana-Champaign, followed by a postdoctoral fellowship at the *in vivo* MR Research Center at NIH. She has served as a faculty member at the Albert Einstein College of Medicine and Georgetown University's Institute for Cognitive and Computational Sciences and Department of Neurology, and Program Director of the Cancer Imaging Program at the National Cancer Institute.

Hyperpolarized ^{13}C MRI has recently attracted much attention. Several research groups have been successful in using this emerging technology in animal studies for various biological applications. In October 2010, Dr. Sarah Nelson, an NIBIB grantee at the University of California, San Francisco

(UCSF), started the first ever human clinical trials of the safety, tolerance, and imaging potential of hyperpolarized ^{13}C MRI with more than 30 prostate cancer patients. This landmark achievement was highlighted in a 2011 issue of *Neoplasia* and is described in detail in her presentation at this Council meeting.

Clinical (proton) MRI detects hydrogen nuclei or protons in water and fat. As a result of the small magnetization, or polarization, of magnetic nuclei (typically only 1 in 100,000 nucleus spins contributes to the MR signal), nuclear magnetic resonance (NMR) and MRI have intrinsically low sensitivity. The high concentration of protons in water in the human body overcomes this low polarization, contributing to clinical MRI's success. Although proton MRS can be used to detect metabolites that contain protons, research extending back to 1979 suggests that ^{13}C MRS is unique among imaging modalities in its ability to probe tissue metabolism, producing more useful metabolic information than proton MRS. In addition, ^{13}C MRS is the only method capable of directly measuring neuronal function of the human brain; in contrast, functional MRI measures neuronal function only indirectly. The first technique to demonstrate impaired mitochondrial function *in vivo* in diabetes and aging brain and muscle, ^{13}C MRS has applications in many areas of medicine, including endocrinology, oncology, and neurology.

Practical limitations of ^{13}C MRS for metabolite detection include low concentration of metabolites (millimolar levels) in the human body, low natural abundance of ^{13}C (only about 1 percent of all carbon atoms are ^{13}C), and low polarization of ^{13}C (the MRS signal of ^{13}C is only one quarter of that of a proton). Low concentration of metabolites cannot be changed, but low natural abundance of ^{13}C and low polarization can be improved. For example, researchers can replace all carbon atoms in natural glucose with ^{13}C. When such labeled glucose is injected into the body, MRS can be used to follow its metabolism (e.g., conversion of glucose into N-acetylaspartate, glutamine, glutamate, and gamma-aminobutyric acid). ^{13}C-labeled lactate and ^{13}C-enabled acetate also can be used. Low polarization can be improved through dynamic nuclear polarization (hyperpolarization), a method that redistributes polarization from electron spins to nuclear spins. Redistributing polarization from electrons to nuclei produces a signal that is 10,000 times stronger. Hyperpolarization, however, is efficient only in extremely low temperatures (1 degree Kelvin). Thawing frozen hyperpolarization solution to a liquid state for biomedical applications had been problematic until 2003, when a group of researchers in Sweden published a practical way to dissolve a frozen solution into a liquid state. With this advance, almost all limitations on the practical use of ^{13}C can, in principle, be overcome.

New MR technologies are being developed to take advantage of the use of hyperpolarized ^{13}C. The hyperpolarization of ^{13}C has shown very good spectral resolution and spectral dynamics in a number of applications in animal models. Researchers already have used ^{13}C bicarbonate to map pH value in tissues; tumor tissue is known to have a lower pH, and pH alterations in other tissues have been linked to a number of diseases. NIBIB grantee Dr. Dirk Mayer has developed rapid MRI sequences that can be used in hyperpolarized ^{13}C MRI to examine how tumors respond to chemotherapy.

^{13}C MRS has a number of advantages over other metabolic imaging methods. Proton magnetic resonance spectroscopic imaging (^{1}H MRSI) provides information on only a limited number of metabolites and gives steady-state concentrations rather than tracer uptake. Fluorodeoxyglucose positron emission tomography (FDG-PET) is already in routine clinical use and being reimbursed by insurance companies. FDG and other radiotracers currently under investigation for use with PET provide only limited biochemical information, making it difficult to determine the fate of tracers in key metabolic pathways. By contrast, ^{13}C MRI gives rich metabolic information in a short period of time—sometimes under one minute. It enables probing of enzyme-specific activities in some of the

key fast metabolic pathways and allows simultaneous polarization of multiple substrates in the same preparation, thereby allowing simultaneous metabolic imaging of multiple pathways. Another advantage over PET is that ^{13}C MRI does not use harmful ionizing radiation. The potential for high-resolution rapid imaging of tissue biochemistry using this emerging technology is enormous.

One of the main limitations of hyperpolarized MR techniques is rapid decay of polarization to an equilibrium state. This occurs in less than a minute. In that short time, researchers must thaw the hyperpolarized substrate and inject it into a patient. The signal continues to decay as it travels through the vasculature until it reaches the tissue of interest. Longer hyperpolarization is needed to image metabolic pathways in real time. Although the substrates used are not foreign to the human body, injecting them at the high concentrations that the technique currently requires could perturb normal physiology, a potential safety concern.

NIBIB has funded several grants to address these challenges, including research to develop new, longer-lifetime substrates, higher levels of hyperpolarization, and optimized data acquisition, analysis, and display. Success in these areas will accelerate clinical translation. NIBIB also has funded the UCSF Hyperpolarized MRI Technology Resource Center, an institution uniquely positioned to advance this field.

Questions and Discussion

Dr. Michael Yaszemski asked whether rapid biochemical imaging with hyperpolarized ^{13}C MR might someday be used clinically in the way standard MRI is used. Dr. Liu responded that standard proton MRI would still be preferred due to its superior spatial resolution and broader application (e.g., perfusion, diffusion, and other physiological imaging based on protons). ^{13}C MR is useful specifically for detecting metabolite spectrum and is considered a supplement to standard MR in the field of metabolism. On the other hand, hyperpolarized protons are unsuitable for metabolic imaging; they decay much more rapidly than hyperpolarized ^{13}C.

Dr. Philip Alderson wondered whether magnetic field strengths higher than 3.0 Tesla would be needed for clinical applications. Dr. Liu noted that Dr. Nelson's group used 1.5 Tesla and 3 Tesla scanners, but the increased field strength did not produce significant gains. Dr. John Gore added that, unlike conventional MRI where higher strength magnetic fields are used to generate high magnetization inside the body, magnetization is independent of field strength in this technique. Hyperpolarization produces increased magnetization of substrates outside of the body and should work well at low field strength.

V. Applications of Hyperpolarized ^{13}C Metabolic Imaging to Cancer: Sarah Nelson, Ph.D.

Dr. Liu introduced Dr. Sarah Nelson, Co-Chair of the Department of Bioengineering and Therapeutic Sciences and Director of the Center for Non-Invasive Imaging and Metabolomics and the Surbeck Laboratory of Advanced Imaging at UCSF. Dr. Nelson is well respected in the fields of metabolic imaging and mathematical modeling, signal processing, algorithm development, and MR.

Dr. Nelson gave a detailed presentation on developing applications of hyperpolarized ^{13}C MR to study cancer metabolism. Dr. Nelson's work in ^{13}C metabolic imaging attempts to improve the sensitivity, specificity, and applicability of MR metabolic imaging; monitor dynamic changes in metabolic processes rather than merely steady-state effects; evaluate metabolism in regions of the body where motion is a time-limiting factor; assess disease activity and contribute to decisions concerning patient care; and develop a platform for following drug effects and evaluating response to therapy.

Characteristics of Hyperpolarized MR

Because polarization decays quickly, shortening the time from thawing to injection is critical. It also is important to know how long it takes the polarizer to reach the target organ once injected. This information is used to select polarizers that decay slowly enough to allow for imaging of the target tissue. For example, to acquire metabolic images of the prostate, one must select a compound that has a polarization lifetime of at least one minute; this greatly limits the metabolic processes one is able to measure.

Another characteristic of hyperpolarized MR is that magnetization decreases after thawing and with each radio frequency pulse, and it cannot be renewed. This limits the number of MR techniques that can be used to measure the signal. Further, because the technique uses injected rather than endogenous substrates, this bolus substrate delivery must be modeled when interpreting results. Modeling changes in signal intensity is difficult because the injected substrate metabolizes into other compounds.

Early Studies

Dr. Nelson's research team has used mouse, rat, and dog models to investigate tumor progression and response to therapy in prostate, brain, and liver cancer, and in bone metastases; to test new MR techniques for improved speed, coverage, dynamic data, and information content; and to develop and investigate new hyperpolarized agents to provide novel metabolic and physiological information.

Dr. Nelson and her colleagues have built on the work of Klaes Golman (Malmö, Sweden), who conducted the first *in vivo* demonstration of ^{13}C MR utility in 2005. Golman imaged a tumor model using ^{13}C-labeled pyruvate, ^{13}C-labeled alanine, and ^{13}C-labeled lactate, proposing that the ratio of lactate to pyruvate would be a measure of abnormal metabolism associated with tumors. In one of Dr. Nelson's early studies using a transgeneic mouse model for prostate cancer (TRAMP), she found that the relative ratio of lactate to pyruvate changes as a tumor progresses; the ratio seems to be proportional to the grade, and therefore aggressiveness, of the tumor. It is possible that, one day, ratios of these metabolites will be used to monitor tumor progression in the clinic. In studies focused on monitoring response to therapy, Dr. Nelson used TRAMP mice and androgen deprivation therapy. Five days after therapy, responders showed a decrease in lactate-to-pyruvate ratio, indicating reduced tumor growth; nonresponders with continued tumor growth actually showed an increase in lactate-to-pyruvate ratio. These clear differences in response were observed much earlier than changes associated with apoptosis and tumor volume. In another study, Dr. Sabrina Ronen used the lactate-pyruvate ratio to look at PI3-kinase inhibition in prostate cancer metastasized to the bone; she determined that changes in lactate-pyruvate ratio are accompanied by changes in LDH and HIF-1 protein expression. Using MYC transgenic mice, Dr. Nelson's colleagues Drs. Dan Vigneron and Andrei Goga combined metabolism and genomics to study the molecular mechanisms of tumor formation in the liver. They observed how alanine, pyruvate, and lactate levels change as tumors form and grow in the liver. Genomic analysis showed that LDH expression increases as tumors grow and decreases as they regress. A study of U85 and U251 glioma models showed a statistically significant difference in the lactate-pyruvate ratio between cancerous and healthy brain tissue. The observed changes are consistent with histology findings. Another study demonstrated that measuring lactate-pyruvate ratio in ^{13}C spectra could be used to monitor response to brain cancer therapy. This rapid assessment could be applied to identify patients who are not benefiting from therapy sooner than would be possible with other methodologies. The implication of these preclinical data is that hyperpolarized ^{13}C imaging is

practical and feasible for *in vivo* studies and can be used to examine tumor grade/aggressiveness and response to a broad range of therapies.

^{13}C MR in Humans

One area that is ripe for further investigation is translation of ^{13}C MR to humans with cancer. Translating ^{13}C MR to human studies involves several components: chemistry preparation, sterile compounding, conduct of an integrated imaging exam, and development of MR scanner hardware and software to work with ^{13}C. UCSF researchers and industry partners can address these various challenges. The chemistry preparation involves agent and radical preparation and selection of the appropriate dissolution medium. Sterile compounding starts with a dynamic nuclear system that polarizes the solution. Next, the radical is removed because it could be harmful to humans if injected into the body. The solution is then loaded into a syringe manually or using an injector. A quality control system ensures proper temperature, pH, and concentration before injection into the subject. The integrated imaging exam component includes performing standard MR imaging before injection. After injection, ^{13}C images are taken. Metabolic data are combined with the anatomic, structural, and vascular data obtained through standard MRI for reference. Because most commercial clinical scanners are not set up to conduct ^{13}C MR routinely, researchers must adjust software and hardware. In addition, radiofrequency coils capable of detecting both proton and carbon frequencies must be designed. New protocols also must be developed, along with pulse sequences and analysis methods.

Dr. Nelson received Food and Drug Administration (FDA) approval in October 2010 to begin the first human clinical study to test the safety, tolerability and imaging potential of hyperpolarized ^{13}C pyruvate injection. The study enrolled more than 30 men on watchful waiting for a biopsy-confirmed prostate cancer. To avoid enrolling patients who might refuse to remain in the scanner, previous experience with an MR exam was required. Three doses of ^{13}C pyruvate were used; at each dose level, three patients were given a dynamic scan and three patients received MR spectroscopy imaging (MRSI). Three additional patients received the maximum tolerated dose (MTD), and 15 additional patients treated at the MTD were studied for biological variation. All patients were required to satisfy all clinical pre-screen tests, be monitored on the day of the exam, and return for a follow-up clinical exam. In total, 31 patients received an injection of hyperpolarized ^{13}C pyruvate that passed quality control tests (i.e., measurement of pH, polarization percentage, and temperature during ^{13}C pyruvate generation). The time from dissolution to injection into patient was critical, because the half-life of hyperpolarized ^{13}C pyruvate is only about 70 seconds; a staff member measured each step with a stopwatch. The total time from beginning dissolution to injection ranged from 43 to 88 seconds, with a mean of 67.6. This particular study used hand injection due to FDA concerns about the proposed automatic injector. All of these processes will be more automated in the future and, therefore, quicker.

Preliminary analysis of the ^{13}C datasets showed the mean times from injection to maximum lactate (42 seconds) and maximum pyruvate (37 seconds) were very fast. The mean signal-to-noise ratios also were excellent (20.4 lactate, 116.4 pyruvate).

The dose escalation phase of the study was completed with no dose-limiting toxicities; the highest dose was selected for subsequent studies. A handful of patients reported experiencing a metallic taste in the mouth, having diarrhea, and feeling abnormal at the time of injection. The one- and two-dimensional dynamic data gave consistent delivery times for pyruvate and lactate in the tumors. The maps of lactate and pyruvate were consistent with prior biopsies, even for the relatively low-grade lesions. In cases where there was evidence of progressive disease on a standard MRI, the ^{13}C

lesion was also much larger. These results have provided a strong rationale for continued development of the technology and expansion to other patient populations.

Hyperpolarized MRI Technology Resource Center

NIBIB funding supports technology development and expansion to other patient populations at the new Hyperpolarized MRI Technology Resource Center at UCSF, where Dr. Dan Vigneron serves as principal investigator. Many hyperpolarized probes relevant to metabolism are under development and have been tested in cell culture and in animals. Dr. John Kurhanewicz is exploring the development of bioreactors that optimize signal acquisition in both cells and human tissue slice cultures; this would help maintain the viability of tissue slices for evaluating new ^{13}C probes to be used as biomarkers for monitoring new therapies and their effects on metabolism. Dr. Sabrina Ronen has developed ^{13}C methods for monitoring 2-hydroxyglutarate in brain tumors with mutated isocitrate dehydrogenase enzyme. She has recently applied for R21 funding to extend these studies. Drs. David Wilson and Kayvan Keshari are working on hyperpolarized ^{13}C probes for monitoring conversion of dehydro-ascorbate to vitamin C in various tumors and neurological diseases. Center researchers also are working on dynamic spectroscopic imaging in order to look at all metabolites simultaneously, as well as developing metabolite-specific echo-planar methodologies.

The Future of Hyperpolarized ^{13}C MR

Dr. Nelson and her colleagues are optimistic that hyperpolarized carbon methodology will become the most reliable way to monitor metabolic abnormality *in vivo*. All of the described studies utilized radio frequency coils with single channels; however, use of multiple detectors would both optimize and minimize acquisition time. Dr. Nelson has been working on multichannel ^{13}C arrays for preclinical studies in mouse and rat models in preparation for human brain tumor studies. Preclinical testing using an auto-calibrated SENSE technique produced thousands of voxels in 13 seconds at a 0.5 cc spatial resolution. Researchers believe that this kind of resolution will be achieved in humans.

The current generation of HyperSense® dynamic nuclear polarization (DNP) polarizers, while suitable for animal research, cannot produce volumes large enough for human testing. General Electric is developing a new polarizer specifically for translation to the clinic. Approximately the size of a refrigerator, the polarizer is self-contained and automated (i.e., no need for multiple operators when generating the compound), and includes a sealed fluid path (i.e., no cold room required). The prototype of this polarizer will be distributed to a number of institutions within the next year.

Hyperpolarized ^{13}C metabolic imaging is an exciting new technology for preclinical and clinical studies. C_1- labeled pyruvate is the first agent being examined, but many other compounds are under evaluation. The first clinical trial of ^{13}C metabolic imaging has been completed with no dose-limiting toxicities in prostate cancer patients. Manufacturers are making HyperSense and SpinLab polarizers available to the MR community to develop new applications. This research is highly collaborative—basic scientists, MR physicists, hardware and software engineers, and pharmacists are all needed.

Questions and Discussion

Dr. Alderson asked how the tracer transit affects signal output, considering the strict time limitations. Dr. Nelson responded that measuring tracer transit time is the first step. The reproducibility of the dynamic data in the clinical trial was rather good. Future studies will focus on changes in signal intensity, perhaps using copolarization with urea and other tracers that can be used

as perfusion tracers. The degree of vascularization and the metabolism itself must be considered. Dr. Alderson suggested measuring the time course of activity over the reference closed vessel—the iliac artery for the prostate, for example—simultaneously with the organ signal, then deconvolving the prostate signal with the arterial signal; Dr. Nelson agreed.

Dr. Buddy Ratner asked about the dissolution process and associated quality control. Dr. Nelson explained that the sample is kept in a solid phase in liquid helium at approximately 1 degree Kelvin inside a magnet. After removal from the liquid helium, a hot liquid under pressure is delivered to the sample, warming it into liquid form. For human acquisitions, the electron donor radical is removed from the sample. During quality control, a small amount of sample is automatically taken to measure polarization, pH, volume, weight, temperature, and color (removal of the radical changes the color of the solution from green to white). The commercial, automated version must include these measurements to ensure safety in humans.

Regarding the prostate cancer study, Dr. Belinda Seto asked whether the patients' prostate-specific antigen (PSA) levels correlated with the measured lactate-pyruvate ratios. Dr. Nelson noted that the data are still being analyzed, and she is not sure whether enough data were acquired in a reproducible way to answer this question. Dr. Seto added that it might also be beneficial to analyze the range of lactate dehydrogenase activity within each of the patient groups; this would be a great biomarker in conjunction with, or perhaps substitution for, PSA. Dr. Nelson added that costs could be reduced by combining anatomic imaging with metabolic imaging in a single 15-minute exam.

Dr. Pettigrew noted that PSA, the one serological biomarker currently used, is notorious for its inaccuracy in predicting malignancy. He wondered whether Dr. Nelson has observed any correlations between metabolites and PSA level or gained any insight into PSA as a biomarker based on the metabolic information. Dr. Nelson remarked that Dr. Kurhanewicz would have more detailed information about proton spectroscopy. Many patients with rising PSA levels have very clear proton spectroscopy abnormalities; the advantage of prescreening with PSA may be in saving cost until a reliable, more expensive imaging exam is needed (e.g., after change in PSA).

Dr. Nola Hylton asked whether Dr. Nelson found any false negatives in the human studies. Dr. Nelson responded that the presence of false negatives could not be verified; her group is reworking a study protocol to examine patients before they go into surgery, using a step-mounted analysis.

Dr. Peter Kirchner asked how the researchers decided on the maximum dose to inject into patients, given that the side effects were negligible. Dr. Nelson stated that the initial toxicity studies were conducted in Europe on a dog model. In this model, the researchers found changes in blood pressure and cardiac function that were associated with delivery of a large bolus of the agent. These findings were supported by abnormalities in blood pressure found in a Finnish study that injected human subjects with ^{12}C pyruvate. In Dr. Nelson's clinical study, the maximum dose was lower than the dose associated with blood pressure changes, although oncologists believe it would have been safe to use an even higher dose. She added that a volume of 30-40 cc is a reasonable amount to inject.

Dr. Gore asked whether the compounds are deuterated. Dr. Nelson replied that they are not. The current market cost of 50 g of ^{13}C pyruvate generated with all the requirements for human use is $10,000, but it is not a good manufacturing practice (GMP) compound; Dr. Nelson's recent order from Sigma-Aldrich for first-GMP pyruvic acid is $30,000 for 100 g, or 40 doses. The current high cost is associated with clean room preparation, sterilization, etc. As the technology becomes widely used, the cost eventually will come down to the cost of a PET exam.

Dr. Pettigrew asked about the sensitivity of Dr. Nelson's in-house acquisition technique. Dr. Nelson responded that there are 30 to 50 HyperSense polarizers in various institutions and other preclinical studies similar to hers. Some of them will use the same sequence. UCSF is making all of the sequences available to the community, including a set that works on high-resolution variant scanners as well as on the General Electric system. The important factor is acquiring the signal as quickly as possible.

VI. Adjournment

The open session of the NACBIB meeting was adjourned at 12:00 p.m.

VII. Closed Session

The grant application 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 1:45 p.m.

Certification:

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

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

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Roderic I. Pettigrew, Ph.D., M.D.
Chairperson,
National Advisory Council for Biomedical Imaging and Bioengineering
Director,
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[2] These minutes will be approved formally by the Council at the next meeting on May 21, 2012, and corrections or notations will be stated in the minutes of that meeting.