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]
DRAFT May 20, 2011

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 26th meeting on May 20, 2011, 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 11:45 a.m. for review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:00 p.m. to 3:00 p.m. for consideration of individual grant applications.

Council members present:
Dr. Gary H. Glover, Stanford University, Stanford, CA
Dr. W. Eric L. Grimson, Massachusetts Institute of Technology, Cambridge, MA
Dr. Hedvig Hricak, Memorial Sloan-Kettering Cancer Center, New York, NY
Dr. Mae C. Jemison, Biosentient Corporation, Houston, TX
Dr. Percival McCormack, University of Illinois at Chicago, Chicago, IL
Dr. Cherri Pancake, Oregon State University, Corvallis, OR
Dr. Buddy Ratner, University of Washington, Seattle, WA
Dr. David Skorton, Cornell University, Ithaca, NY
Dr. Michael Yaszemski, Mayo Clinic College of Medicine, Rochester, MN

Ex officio members present:
Dr. Andrew Watkins, Centers for Disease Control and Prevention, Atlanta, GA

Council members absent:
Dr. Philip Alderson, Saint Louis University, St. Louis, MO

Ex officio members absent:
Dr. Francis Collins, National Institutes of Health, Bethesda, MD
Dr. John McGrath, National Science Foundation, Arlington, VA
Dr. P. Hunter Peckham, U.S. Department of Veterans Affairs, Cleveland, OH
Dr. Anne Plant, National Institute of Standards and Technology, Gaithersburg, MD
Ms. Kathleen Sebelius, U.S. Department of Health and Human Services, Washington, DC
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences, Bethesda, MD

Chairperson:
Dr. Roderic I. Pettigrew

Executive Secretary:
Dr. Anthony Demsey

[1] For the record, it is noted that members absent themselves from the meeting when the Council is discussing applications (a) from their respective 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.

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

Mr. Angelos Bacas
Dr. Richard A. Baird
Ms. Barbara Cantilena
Ms. Patty Clements
Ms. Shirley Coney-Johnson
Dr. Richard Conroy
Ms. Zoe-Ann Copeland
Ms. Nancy Curling
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
Ms. Jude Gustafson
Dr. John Haller
Dr. John Hayes
Ms. Eunica Haynes
Dr. William Heetderks
Dr. Lori Henderson
Dr. Rosemarie Hunziker
Dr. Thomas Johnson
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Peter Kirchner
Dr. Brenda Korte
Dr. Richard Leapman
Mr. Eugene Lee
Dr. Guoying Liu
Dr. Hector Lopez
Dr. James Luo
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Larry Morton
Dr. Grace Peng
Dr. Karen Peterson
Ms. Vicki Rein
Ms. Stephanie Sabourin
Dr. Belinda P. Seto
Mr. Shaun Sims
Dr. Paul Smith
Dr. Manana Sukhareva
Ms. Florence Turska
Mr. Kwesi Wright
Ms. Li-Yin Xi
Dr. Ruixia Zhou

Non-NIBIB NIH employees:
None

Non-NIH Federal employees:
None

Members of the public present for portions of the meeting:
Dr. Linda Griffith, Massachusetts Institute of Technology
Ms. Allyson Harkey, NOVA Research Company
Ms. Masako Kaufman, Iri Sangyo Shimbun
Ms. Jeanie Kennedy, American Academy of Orthopedic Surgeons
Mr. Vhic Mata, Event Technology Solutions
Mr. Stephen Murphy, IQ Solutions
Mr. Matt Sherman, National Capital Captioning
Mr. Brian Washington, Event Technology Solutions

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey called to order the 26th 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. Outgoing Council Members

Dr. Pettigrew expressed gratitude to outgoing Council members Drs. Gary Glover, Mae Jemison, and Percival McCormack, thanking them for their service. All will receive a memento of their participation on the Council.

B. New Council Member

Dr. Pettigrew introduced new Council member Dr. Michael Yaszemski, a professor of biomedical engineering and orthopedics at Mayo Clinic. His research areas of focus are tissue engineering and biomaterials (specifically spinal cord regeneration), musculoskeletal sarcoma biology, and translational research.

C. Awards

Dr. Pettigrew acknowledged honors bestowed upon members of the NIBIB community. Dr. Harry Barrett, an NIBIB MERIT Awardee, received the SPIE Medical Imaging Gold Medal and the Institute of Electrical and Electronics Engineers Medal for Innovations in Healthcare Technology. Dr. Justin Hanes, Edward C. Nagy New Investigator Awardee, was elected to the Global Young Academy of the National Academies of Science. Dr. Mark Prausnitz, Quantum Awardee, received the 2011 Outstanding Achievement Award in Research Program Development at the Georgia Institute of Technology. Dr. Pettigrew congratulated Council Member Dr. Eric Grimson on his recent appointment as Chancellor of the Massachusetts Institute of Technology (MIT).

D. Budget

Dr. Pettigrew reported that the number of high-scoring applications had increased between 60 and 100 percent in the last four funding cycles. However, the number of such applications to be reviewed at today's meeting is similar to that of May 2009. The reason for this decrease is unclear, as was the reason for the 2010 increases. NIBIB will continue to monitor these trends.

The 2011 NIBIB budget, resulting from the continuing resolution, includes a 1-percent reduction in funding from 2010. The grant payline for established investigators will be at the 11th percentile; for new investigators, that payline will be 16 percent.

E. Key Conferences

a. Edward C. Nagy New Investigator Symposium

The first Edward C. Nagy New Investigator Symposium featured eight outstanding NIBIB-funded new investigators studying a diverse range of topics. The Symposium will be held periodically to highlight cutting-edge research by young investigators supported by NIBIB.

b. Summit on Management of Radiation Dose in Computerized Tomography

The *Summit on Management of Radiation Dose in Computerized Tomography: Toward the Sub-mSv Exam* was held February 24–25 with the cosponsorship of the Coalition for Imaging and Bioengineering Research; the U.S. Food and Drug Administration (FDA); the American College of Radiology; the American College of Cardiology; the Eunice Kennedy Shriver National Institute of Child Health and Human Development; the National Heart, Lung, and Blood Institute; and the National Cancer Institute. The Summit focused on transforming computerized tomography (CT) technology and its use toward a specific goal of reducing the routine CT exam dose to below one mSv. Achieving this goal would serve to minimize public health risks from radiation exposure. The Summit was particularly timely, as an article in *Science*, a landmark special report in the *Journal of Radiology*, and sessions at the annual meeting of the Society for Imaging Informatics in Medicine all recently focused on CT dose as a national

public concern. A manuscript for journal publication is being prepared, and Dr. Pettigrew anticipates developing an initiative in this area.

F. New NIBIB Initiatives

Recently released new initiatives include a Request for Applications that focuses on the development and translation of medical technologies to reduce health disparities, Program Announcements for R01s and R21s on nanoscience and nanotechnology in biology and medicine, and a Program Announcement with special review (PAR) focused on predictive multiscale models for biomedical, biological, behavioral, environmental, and clinical research. The PAR is jointly sponsored by the Department of Defense, the National Science Foundation, and the Food and Drug Administration.

G. NIH Plain Language Awards

NIBIB received two NIH Plain Language/Clear Communication Awards in May. These awards are given annually to honor outstanding communication products that exemplify NIH's commitment to effective public communication. An e-Advance highlighting a tongue-operated device to control wheelchair operations for paralyzed patients won a Gold Award, and the new NIBIB marketing brochures received a Silver Award. Dr. Pettigrew acknowledged Mary Beth Kester, Cheryl Fee, and NOVA Research Company for their work on these award-winning publications.

H. NIH Update

The National Center for Advancing Translational Sciences (NCATS) is scheduled to open in fiscal year 2012. In response to discussions with the extramural community, its mission now focuses on "catalyz[ing] the development of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions." NCATS will facilitate, rather than duplicate, other NIH-supported translational research activities; complement, rather than compete with, the private sector; and reinforce NIH's commitment to translational science.

NIH recently announced the selection of Dr. Martha J. Somerman as Director of the National Institute of Dental and Craniofacial Research. Dr. Somerman is currently Dean of the University of Washington School of Dentistry and will assume her new post at the end of August.

I. Research in the News

Dr. Pettigrew described three research advances by NIBIB grantees. Dr. Quyen Nguyen is using molecularly-targeted fluorescent cell-penetrating peptides to deliver targeted therapeutics and diagnostics to cells of interest. The peptides mark tumors and nerves with different colors, thereby allowing a surgeon to distinguish between the two tissue types.

Dr. Kullervo Hynynen has developed the world's first magnetic-resonance-guided high-intensity ultrasound that focuses on specific targets within the brain. The initial work, funded under an R01, was intended for use in the treatment of brain tumors. The technology is being applied in an FDA trial recently begun at the University of Virginia.

Dr. Michael Goldfarb has developed a prosthesis that powers both the knee and ankle and facilitates more natural motion, providing the patient with increased balance, agility, and recovery reflexes.

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 member Dr. Philip Alderson was unable to attend. 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, the NACBIB meeting is open to the public for all except the review of individual grant applications. Dr. Demsey reviewed conflict-of-interest, confidentiality, and lobbying guidelines.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for Monday, September 12, 2011, 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 January 24, 2011, NACBIB Meeting Minutes

A motion to approve minutes of the January 24, 2011, NACBIB meeting was forwarded, seconded, and approved unanimously.

IV. Strategic Plan Implementation: Dr. William Heetderks

Dr. Heetderks announced that the draft Strategic Plan had been posted to the NIBIB Web site for public comment the day before this meeting. The goals of the draft NIBIB Strategic Plan are as follows:

1. Improve human health through the development of emerging biomedical technologies at the interface of engineering and the physical and life sciences.
2. Enable patient-centered health care through development of health informatics and mobile and point-of-care technologies.
3. Transform advances in medicine at the molecular and cellular levels into therapeutic and diagnostic technologies that target an individual's personal state of health.
4. Develop medical technologies that are low cost, effective, and accessible to everyone.
5. Develop training programs to prepare a new generation of interdisciplinary engineers, scientists, and health care providers.
6. Expand public knowledge about the medical, social, and economic value of bioengineering, biomedical imaging, and biomedical informatics.

In order to determine its success in achieving these goals, NIBIB will need to assess impact on health care, society, the economy, knowledge and technology, and the next generation. Dr. Heetderks outlined three possible assessment approaches: real time, prospective, and retrospective.

One real-time measure of NIBIB impact involves analyzing grantee publications; for instance, over the last five years, the total number of publications from NIBIB grantees per year has increased from approximately 1,300 to 3,300. Another real-time measure of impact involves examining the focus of NIBIB's research investments and how this has changed over time. In the past five years, funding via R01s increased approximately 5 percent, Bioengineering Research Partnerships (BRPs) increased approximately 3 percent, and R21s decreased approximately 7 percent. Investment by program area also changed during this 5-year period; funding of R01s and R21s in bioinformatics increased by approximately 80 percent; funding for ultrasound, tissue engineering, image processing, and image-guided therapies also increased over time; and funding decreased for magnetic resonance imaging/magnetic resonance spectroscopy, nuclear medicine, and medical devices and implants.

A retrospective assessment approach would look at an existing successful drug and trace back the significant points in its development and translation to market, noting where those points can be applied

to early-stage drugs today. Although it is important to know that NIBIB grantees have obtained 141 patents in the past five years, it is equally informative to know how many license agreements have been signed, new and approved products developed, jobs created, and lives improved.

Prospective assessment approaches consider the value of information in predicting what will happen in the future. Dr. David Melzer (University of Chicago) is studying the probability that current research will lead to particular results, and the NIH Office of the Director is considering developing infrastructure to collect data relevant to these assessments. Science and Technology for America's Reinvestment: Measuring the Effect of Research on Innovation, Competitiveness and Science (STAR METRICS), a multi-agency venture led by NIH, the National Science Foundation, and the White House Office of Science and Technology Policy, will provide another retrospective assessment approach.

In the last five years, NIBIB has implemented its goals by supporting investigator-initiated applications, providing special funding for new investigators, and using targeted PARs to support initiatives in areas without dedicated funding. The Quantum Grants Program, expanded international activities, and initiatives in point of care, therapeutic ultrasound, technologies for the underserved, and image-guided therapy have all helped move NIBIB toward its goals. Infrastructure support, particularly in the imaging community, will continue to underwrite future research.

Dr. Heetderks invited the Council to discuss implementation of the Strategic Plan over the next few years.

Discussion

Dr. Skorton noted that the Strategic Plan goals may be at a level that is too high to be easily quantifiable. For example, it would take generations to measure improvements in human health. NIBIB and the Council must ensure that selected metrics show whether NIBIB has fared well for federal appropriations and allocations within the NIH budget and whether grantees have subsequently produced recognizable research results.

Dr. Skorton remarked that goal 1 is NIBIB's vision rather than a specific goal. The overall purpose of NIH is to understand life process in health and disease and improve human health. Different Institutes achieve that via different activities; NIBIB achieves it by bringing disciplines together.

Dr. Pettigrew agreed that goal 1 is essentially NIBIB's "bread and butter," but omitting it from the Strategic Plan might signal that the Institute does not support work that is, in fact, central to its mission. At the previous Council meeting, the consensus was that it should be retained as a goal. Dr. Skorton suggested that the goal be changed to an overarching goal, with objectives and strategies beneath it. Dr. Pancake suggested splitting goal 1 into a broad vision statement ("improve human health through advances at the interface of engineering in physical and life sciences") and a specific goal ("develop new technologies…"). Dr. Yaszemski added that any overarching statement should begin with "improve human health."

Dr. Glover stated that "support the development of emerging technologies…" without "improve human health" is measurable.

Dr. Yaszemski proposed that the latter part of goal 1 ("emerging biomedical technologies at the interface of engineering and the physical and life sciences") should be combined with goal 4. Dr. Jemison added that low cost (goal 4) is a very specific kind of technology, distinct from the engineering highlighted in goal 1; if the phrase from goal 1 is moved to goal 4, low-cost technology and emerging biomedical technologies should be listed as separate sub-bullets.

Dr. Jemison suggested changing "develop" in goal 5 to "foster" in order to highlight the many layers of encouraging and stimulating training.

Dr. Skorton suggested changing "expanding public knowledge" to "disseminate information to the public" to make goal 6 quantifiable.

Dr. Skorton suggested that NIBIB host periodic mini-retreats for NACBIB to assess progress so that results could be reported the NIH Director.

Dr. Grimson encouraged taking a broad approach when selecting metrics to measure impact; it is easy for people to focus on metrics rather than actually doing what is necessary to achieve impact. For instance, NIBIB should consider open sourcing appropriate technologies; many communities will not pursue patents, and impact can be great with open sourcing.

Dr. Jemison noted that the goals in the plan may be too diffuse. NIBIB should focus on doing work that other Institutes do not support; for instance, developing tools that are necessary for other research to move forward. Dr. Heetderks noted that other Institutes want to use technology to achieve their missions, but they do not want to develop technology; NIBIB develops technology.

Dr. Pancake suggested thinking of initiatives as rolling over into new work, such as jumpstarting a new area of transdisciplinary research. Dr. Ratner offered that starting with the impact of an area/topic and then working backward to what initiatives should be funded might be a good idea.

Dr. Glover added that funding allocations are particularly important in the current era of declining budgets. With three different foci—investigator-initiated research, intramural research, and targeted initiatives—there is a critical problem of how to allocate funding to best support NIBIB's goals. If the Institute is to be assessed based on funding of programmatic initiatives, the distribution of resources becomes even more important. Perhaps in the future, the Council could have a larger voice in this kind of strategic planning.

Dr. McCormack stated that efforts to develop low-cost devices are completely defeated by the actual profit-making of manufacturers. There is already an incentive to improve the cost and effectiveness on the research end, but cost to the patient is also important.

Dr. Griffith noted that engineering involves analyzing systems for understanding. When discussing technology development, NIBIB should keep in mind that engineering can also improve understanding of the operating principles of biological systems and interventions.

V. Integration of Systems Biology and Tissue Engineering: Linda Griffith

Dr. Pettigrew introduced Dr. Linda Griffith, professor of biological engineering at the Massachusetts Institute of Technology (MIT). Dr. Griffith is chair of the School of Engineering Teaching and Innovation and director of the new Center for Gynepathology Research. Her work focuses on tissue engineering, specifically the design of biomaterials and scaffolds to control the behavior of cells and tissues in order to direct large-scale tissue growth and tissue regeneration. Dr. Griffith has developed a clinically successful scaffold that has been used for regenerating bone.

Dr. Griffith described her work using mathematical models to understand biology and translate that understanding into building new tissue. In the past, therapeutic tissue engineering (i.e., using cell-based approaches to replace organ tissue) has been emphasized. Dr. Griffith's laboratory, funded in part by a NIBIB Transformative R01 grant, instead works to understand disease and drug development through complex models to eliminate the need for many regenerative medicine technologies. Although mathematical and/or physical modeling is often viewed as the domain of only mathematicians and physicists, engineers also use mathematics and physics to solve complex problems. In engineering cell biology, there is an emerging interest in analyzing biological systems and developing a framework upon which to design blueprints.

Idiosyncratic hepatotoxicity (in which a drug that was nontoxic in early clinical testing suddenly causes serious, even fatal, toxicities in some patients in large clinical trials) is a challenging problem in drug development. The causes of idiosyncratic hepatotoxicity are not well understood. Some researchers hypothesize that a synergy of drug metabolism (some drugs increase gut permeability) and infection leads to liver toxicity.

To model idiosyncratic hepatotoxicity, Dr. Griffith examines the effects of the drug, soluble cytokines, viral infections, and other stressors on a single cell. Next, she imposes mathematics on the model to understand the system and predict how it would behave in environments where inaccessibility or expense precludes repeated measurement.

The conceptual premise is that extracellular cues, such as drugs and cytokines, trigger measurable intracellular signaling responses. Dr. Griffith is attempting to identify relationships that might apply across a whole universe of potential drug-cytokine interactions. First, various signaling networks (e.g., Akt, JNK, IKK, MK2) inside the cell are activated by extracellular cues. Dr. Griffith distributes the measurements of changes in the cell across all networks that might be affected and measures several nodes within the networks; in this way, the link between a particular response and a particular signal becomes apparent. The model considers a very broad range of network cues in order to drive the cell to the extremes of states it may experience in the body. This model eliminates the need for future researchers to repeatedly conduct all of the measurements against all of the cues.

To identify relational variables, Dr. Griffith used three cell culture systems: primary rat hepatocytes, primary human hepatocytes, and the HepG2 cell line. Various cytokine mixtures were used to stimulate inflammation, and idiosyncratic toxic and nontoxic drugs were tested. Seventeen phosphoproteins across multiple signaling networks were measured at two time points; cell death was measured by two methods. Dr. Griffith observed a supra-additive synergy between some drugs and cytokines; more cell death was observed with drug-cytokine combinations than with either cytokine alone or drug alone. To see whether the observed synergy applied more broadly, students in Dr. Griffith's laboratory extended the experiment to include 90 drugs from Pfizer's drug-induced liver injury list; performance in the clinic is already known for most of these drugs. They observed synergy between many of the drugs and cytokines below the maximum/peak concentration of drug.

Dr. Griffith postulated that, if there is a universal way that these drugs induce toxicity, it might be possible to treat at-risk patients to prevent the toxicity. To explore this idea, her team measured 17 phosphoproteins that may intersect with the metabolism of drugs at different time points and with different drugs, cytokines, growth factors, and cell cycle signals. After analyzing the resulting data set for a consensus relationship between signals and outcomes, the researchers determined that the responses were multivariate. Working with Dr. Doug Lauffenburger's laboratory at MIT and researchers at Pfizer, orthogonal partial least-squares modeling was employed to deconvolve and identify principal components emerging from the signaling data set and their relationship to the phenotype. The analysis revealed that four signaling networks were strongly correlated with the phenotypes; two networks were associated with a pro-survival kinase (Akt and mTOR), and two were associated with a pro-death kinase (MEK/ERK and p38/MK2). The findings were validated using a leave-one-out method against the data set.

Dr. Griffith tested the model in cells from two donors subjected to the same conditions; the model was first trained on cells from one donor and then applied to cells from the second donor. The four-network model accurately predicted signal-response relationships across multiple hepatocyte donors. The model was then tested in cells from the second donor under conditions not used in the training set. Drug concentration thresholds were chosen so that potentially toxic drugs would pass the first screen. The model revealed that there is a consensus network among the drugs used and that autocrine loops cause either pro-death or pro-survival signaling. TNF sets off a set of negative feedback autocrine loops involving IL-1 and shedding of the EGF receptor ligand. These findings give researchers the opportunity to understand mechanistically how cytotoxicity occurs. The EGF receptor was often activated in the cytokine-induced networks. Although the simple-cell culture model did not capture all of the toxic drugs, it is useful as a primary screen.

In order to adequately capture complexity beyond the scope of the simple-cell culture models, Drs. Griffith and collaborator Steven Tannenbaum (MIT) have spent the past ten years developing a three-dimensional model that uses a microfabricated profusion reactor and a tissue unit roughly the size of

a capillary bed. A thin scaffold captures cells and induces them to reorganize into tissue-like structures, resulting in some facets of tissue structure and many facets of tissue function. The system has oxygen gradients, which is useful because many toxicities occur due to gradients in the tissue. In collaboration with Pfizer, Amgen, and Roche, Dr. Griffith adapted this model to a high-throughput, multiwell-plate format that uses a microfluidic pump to pump fluid at a desired rate (e.g., arterial flow rate, interstitial fluid rate). When the researchers examined how flow rates affect the biology of the tissue, they found that high flow rates enhance stellate cell prevalence relative to sinusoidal cells, which is consistent with *in vivo* observations.

The EGF receptor has multiple ligands, all of which are made as transmembrane precursors that can be cleaved by proteases. Certain stimuli (e.g., mechanical stress) can activate proteases that cleave the ligand and thereby transactivate the EGF receptor network. The matrix can act as a depot or sink for ligands. Cells release a ligand, it interacts with the matrix, and whether the ligand returns or not conveys information about the environment to the cell. For example, the ligands HER4 and HB-EGF interact with the EGF receptor on the cell surface and the matrix.

Currently, researchers have almost no way of measuring these extracellular networks. To address this problem, Dr. Griffith initiated a multi-investigator project. Draper Labs, which is expert in microfluidics, was engaged to build environments to macroscopically control the cells. Dr. Paula Hammond, a polymer scientist, and others were involved in creating biomaterials onto which probes could be attached to measure cytokines locally. A laboratory in California used aptamers to measure cytokines *in situ*. In collaboration with Drs. Barbara Imperiali and Dane Wittrup, Dr. Griffith screened common libraries to find affinity probes that recognize their target and labeled those affinity probes with solvatochromic fluorophores that are dark in an aqueous environment and bright in a nonpolar environment. The Imperiali laboratory has developed new labels that are much brighter and more stable under extreme conditions.

Dr. Griffith used yeast surface display in which ScFv was fused to a mating adhesion receptor. Using mating protease, different clones are expressed on the surface of yeast cells, and an epitope tag indicates the level of expression. The ligand is added, and the library is screened for high-affinity binders. Cells are sorted by expression level using flow cytometry.

The Imperiali laboratory had previously used these probes to look at protein-protein interactions, but only via spectroscopy. The Griffith laboratory is now examining whether these probes would work as imaging agents, starting with a well-characterized probe from Dr. Imperiali's laboratory.

The laboratory is attempting to link systems biology with tissue engineering approaches by bringing in new tools and making them available to the community. The Gynepathology Center is using the same approaches in efforts to understand the etiology of endometriosis.

Discussion

Dr. Skorton stated that Dr. Griffith's work exemplifies the way NIH supports both basic and translational research. The knowledge gained from this work will help scientists understand cell biology as well as theory during applied, practical, economic development-related issues. Basic science, pathology, and, eventually, *in vivo* imaging may benefit from this important research.

Dr. Skorton expressed concern about the fibrotic response at high flow rates. Dr. Griffith responded that the flow rate can be controlled independently. The response to the flow rate closely mimics what is seen *in vivo*. The model includes CD-31+ endothelial cells that are observed in patients who develop cirrhosis. Modulating the flow rate captures some facets of this complex integrative response.

Dr. Griffith noted that the research team is also interested in the mechanical stress component because there are problems with fibrotic matrices in breast cancer; the laboratory is attempting to develop matrices

wherein the mechanical properties and permeability can be independently controlled. Drug companies are interested in this type of modeling of disease states, which cannot be replicated adequately in animals.

Dr. McCormack asked whether material elasticity affects mechanical stress. Dr. Griffith responded that a ligand on a tether will behave differently from one that is rigidly fixed on a gel. There are two sources of mechanical stress: the nature of the surface to which the cells are fixed and the rate of the flow through the tissue.

Dr. Ratner asked how different macrophage phenotypes affect cellular responses. Dr. Griffith reported that the endometriosis project is exploring the nature of cells in the peritoneal cavity and is gathering profiles of cytokines in the peritoneal fluid. Dr. Chris Love at MIT is investigating how cells of different phenotype secrete cytokines.

Dr. Hunziker asked about modeling conducted by pharmaceutical companies versus academic laboratories. Dr. Griffith responded that drug companies want to know how to obtain information from a system as cheaply and quickly as possible. Performing difficult assays on numerous components can become prohibitively expensive. Dr. Griffith hopes her research team will have multiple tools that others will use. Combining systems biology and tissue engineering is still an academic exercise.

Dr. Pettigrew asked Dr. Griffith to elaborate on the fibrotic response phenomenon, which seems paradoxical. Dr. Griffith explained that flow decreases in a fibrotic liver because the capillaries are stiffer and narrower. When a person exercises, the blood pressure and pulse go up; the flow also rises, but the vessels relax (dilate) and more arterials open to perfuse the tissue. There is a dynamic cross-sectional area against which blood flows in the body. In contrast, no arterials open and close in Dr. Griffith's system, such that the flow is constant.

Dr. McCormack remarked that, if the stress increases too much, elasticity is reduced, which changes the plasticity. This work may also provide information for interpreting images generated by magnetic resonance, elastography, and other techniques that examine specific tissue properties.

Dr. Pettigrew asked whether flow mediates permeability. Dr. Griffith said that, in their experiments, they add lipopolysaccharides (LPS) to mimic a leaky gut. If immune cells were present in the cell culture, the LPS would activate them. *In vivo*, gut permeability can be compromised by infection.

Dr. Seto asked Dr. Griffith whether she plans to examine drug responses in populations of patients with genetic modifications. Dr. Griffith responded that the breast cancer she had in 2010 was a type (triple negative) that does not respond to any available targeted therapy. Even though the tumor overexpresses the EGF receptor, it does not respond to EGF-receptor-targeted therapies. Certain genetic mutations in the EGF receptor are associated with a high response rate to a particular drug. Surprisingly, 20 to 30 percent of patients who do not have that mutation still respond to the kinase inhibitor. Systems biology approaches reveal that the mutation affects the way the EGF receptor is internalized and recycled. Because tumors are inherently complicated, researchers use combinations of therapies and are attempting to understand where they should focus in the network. Combination therapy may sound appealing, but dramatic side effects can occur.

VI. Adjournment

The open session of the NACBIB meeting was adjourned at 11:45 a.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 3:00 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,
National Institute of Biomedical Imaging and Bioengineering

[2] These minutes will be approved formally by the Council at the next meeting on September 12, 2011, and corrections or notations will be stated in the minutes of that meeting.