National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

June 6, 2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL ARTHRITIS AND MUSCULOSKELETAL
AND SKIN DISEASES ADVISORY COUNCIL

MINUTES OF THE 65th MEETING

June 6, 2008
8:30 a.m. to 5:00pm

I. CALL TO ORDER

The 65th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on June 6, 2008, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 10. The meeting was chaired by Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Attendance

Council members present:

Mr. George Beach
Dr. S. Wright Caughman
Dr. Gena Carter
Ms. Carmen Cheveres
Dr. Betty Diamond
Dr. B. Lee Green (by telephone)
Dr. Kathleen Green
Dr. Bevra H. Hahn
Dr. Joshua Jacobs
Dr. John H. Klippel
Ms. Ann Kunkel
Dr. Lawrence G. Raisz
Dr. Clifford J. Rosen
Dr. H. Lee Sweeney
Dr. James Weinstein (by telephone)

Council members not present:

Dr. Kevin Campbell
Dr. Martin J. Kushmerick
Ms. Patricia McCabe

Staff and Guests:

The following NIAMS staff and guests attended:

Staff

Dr. Janet Austin
Dr. Carl Baker
Ms. Susan Bettendorf
Dr. Michael Bloom
Dr. Amanda Boyce
Mr. Gahan Breithaupt
Dr. Eric Brown
Dr. Branden Brough
Mr. Richard Clark
Ms. Wilma Peterman Cross
Ms. Robin Diliello
Ms. Teresa Do
Dr. Jonelle Drugan
Ms. Sharon Fair
Ms. Barbara Footer
Ms. Valerie Green
Ms. Gail Hamilton
Mr. Andrew Jones
Dr. Daniel Kastner
Dr. Stephen Katz
Ms. Shahnaz Khan
Mr. Mark Langer
Dr. Gayle Lester
Dr. Helen Lin
Ms. Anita Linde
Ms. Mimi Lising
Ms. Leslie Littlejohn
Dr. Kan Ma
Dr. Marie Mancini
Dr. Kathryn Marron
Ms. Melanie Martinez
Dr. Joan McGowan
Ms. Regina Mong
Ms. Melinda Nelson
Ms. Anna Nicholson
Dr. Glen Nuckolls
Dr. James Panagis
Dr. Paul Plotz
Ms. Natalie Reyes
Ms. Trish Reynolds

Dr. Louise Rosenbaum
Ms. Karin Rudolph
Dr. William Sharrock
Ms. Sheila Simmons
Ms. Theresa Smith
Ms. Allisen Stewart
Ms. Yen Thach
Mr. Michael Toland
Ms. Marcia Vital
Dr. Fei Wang
Dr. Yan Wang
Dr. Chuck Washabaugh
Mr. Elijah Weisberg
Ms. Candice Williams
Mr. Carlos Yancy

Guests

Mr. Michael Bykowski, Consolidated Solutions and Innovations
Ms. Diane Christianson, Scleroderma Foundation
Ms. Jodie Curtis, National Psoriasis Foundation
Ms. Christy Gilmour, American Academy of Orthopaedic Surgeons
Ms. Patti Brandy Hansberger, Office of Legislative Policy and Analysis, NIH
Dr. Anthony Hayward, National Center for Research Resources, NIH
Mr. Jésus Lopez, United Planning Organization
Mr. Dawayne Nutt, Office of the Director, NIH
Ms. Jennifer Taylor McBride, Arthritis Foundation
Ms. Sheila Rittenburg, National Psoriasis Foundation
Dr. Lawrence Tabak, National Institute of Dental and Craniofacial Research, NIH

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept with no changes the minutes of the 64th Council meeting, held on January 29, 2008.

III. FUTURE COUNCIL MEETING DATES

Future Council meetings are currently planned for the following dates:

September 23, 2008
February 3, 2009
June 2, 2009
September 16, 2009
February 2, 2010

June 15, 2010
September 8, 2010

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz welcomed Council members, NIAMS staff, and guests. He began his report by noting that Dr. Joan McGowan, Director of the NIAMS Division of Musculoskeletal Diseases, was serving as the Acting Executive Secretary for the Council during this meeting. Dr. Katz invited attendees to review the NIAMS Shorttakes online, which include more detail on many of the topics covered in his report. He noted that his "Director's Column" focuses on peer review at the NIH. Dr. Katz also noted that Council members Dr. Kevin Campbell, Dr. Martin Kushmerick, and Ms. Patricia McCabe were unable to attend the meeting. Two Council members, Drs. Lee Green and James Weinstein, participated in the meeting via teleconference.

Before beginning his formal remarks, Dr. Katz recognized and thanked three members of the NIAMS research community who also are Principal Investigators (PIs) in the NIH Clinical and Translational Science Awards (CTSA) Program: (1) Dr. Frank Arnett, who leads the Center for NIAMS Supported Center for Research Translation in Scleroderma at the University of Texas Medical School at Houston; (2) Dr. Dan Clauw, a rheumatologist who leads an active program in clinical and translational medicine at the University of Michigan Medical School. Dr. Arnett attended the meeting in person; Drs. Clauw participated via teleconference.

Personnel Changes at the NIH and NIAMS

At the NIH level, Dr. Francis Collins, Director of the National Human Genome Research Institute (NHGRI), announced that he will be stepping down as of August 1, 2008, to explore writing projects and other professional opportunities.

At the Institute level, the search for a NIAMS Deputy Director is ongoing; an update may be given at the September Council meeting. Dr. Katz announced that Ms. Marcia Vital has been selected as the Deputy Director of the NIAMS Office of Communications and Public Liaison (OCPL). Ms. Melanie Martinez will be joining the OCPL as a Public Liaison Officer and as a Writer/Editor. Also joining the OCPL is Mr. Carlos Yancy, a Writer/Editor who also will be working on community outreach projects. In the NIAMS extramural program, Mr. Andrew Jones has joined the Institute as the Deputy Grants Management Officer. Ms. Leslie Littlejohn has joined the NIAMS as a Grants Management Analyst, and Ms. Katie Joffee has joined the Institute as an Administrative Grants Management Fellow.

Dr. Katz announced that several NIAMS staff members have been recognized by the NIH community or by their respective professional societies for their exceptional work. Mr. Gahan Breithaupt, the Associate Director for Management and Operations at the NIAMS, received the Supervisor/Program Manager of the Year Award from the Eastern Region of the International Public Management Association for Human Resources. Dr. Alasdair Steven, Chief of the NIAMS Intramural Laboratory of Structural Biology Research, received the Microscopy Society of America's 2008 Distinguished Science Award for the Biological Sciences. In addition, a

number of NIAMS staff were recognized at the NIH 2008 Plain Language Awards Ceremony in April 2008. Ms. Julie Townshend, Dr. Janet Austin, and Ms. Trish Reynolds of the NIAMS OCPL received a Gold award for the bilingual booklet *Isabel's Story: How She and Her Family Learned About Osteoporosis and Bone Health*. Communications staff members Ms. Betsy Lordan, Ms. Leslie McIntire, Ms. Karin Rudolph, and Mr. Richard Clark received a Silver award for *Lupus: A Patient Care Guide for Nurses and Other Health Professionals*. Dr. Jonelle Drugan and Ms. Anita Linde in the NIAMS Office of Science Policy and Planning, along with staff from the National Cancer Institute and the Department of Health and Human Services (DHHS) Office of General Counsel, received a Silver award for the Memorandum of Understanding between the NIH and National Aeronautics and Space Administration (NASA) for Cooperation in Space-Related Health Research that was signed on Capitol Hill last year by NIH Director Dr. Elias Zerhouni and NASA Administrator Dr. Michael Griffin. Dr. Katz also reported that 17 NIAMS staff members will be named as recipients of NIH Director's Award for outstanding contributions to the Institute and to the NIH overall. Included in these awardees is Dr. Paul Plotz, the NIAMS Acting Deputy Director, who will be receiving the NIH Director's Mentoring Award.

Update on Budget and Congressional Activities

At the time of the last Council meeting, the Institute had just received an NIH appropriation for fiscal year (FY) 2008, and specific funding policies were still being developed. These policies have now been established, can be shared, and are available online. A continuing priority is to ensure the availability of an adequate pool of funds for new and competing continuation awards; therefore, the inflationary adjustment for existing noncompeting awards in FY 2008 will be limited to an average of 1 percent. This means most noncompeting awards will receive a reduction of approximately 2 percent below the commitment level, which will be applied to all remaining years of the grant. Dr. Katz explained that as was the case last year, funding priority will be given to new investigators, and the NIAMS will continue the policy of allowing a 3 percent payline differential for these investigators. All established paylines and funding policies for the NIAMS can be found in the FY 2008 funding plan on the NIAMS Web site.

On May 22, the Senate passed the FY 2008 supplemental appropriations bill to fund the wars in Iraq and Afghanistan by a vote of 70-26. The Senate passed an amendment to its version of the bill with funds for domestic programs, including $400 million for the NIH. This bill has now been returned to the House for action and bears little resemblance to the original House-passed version. Specifically, the Senate version does not provide offsets that would pay for additional spending (such as the $400 million for the NIH).

Dr. Katz reported that the Senate adopted the FY 2009 Budget Resolution Conference Report by a vote of 48-45 on June 4, 2008. The House followed suit the next day, by a vote of 214-210. This represents the first budget resolution adopted in an election year since 2000. The resolution is important in that the totals for spending for each of the House Appropriation Committees were supplied, and appropriators may now begin to mark up their respective bills. The Resolution call for $24.5 billion more in discretionary spending than President Bush requested and shows the

budget returning to surplus by FY 2012. This budget resolution is intended to serve as a "blueprint," not as a law.

The FY 2009 President's budget for the NIH remains essentially flat at $29.5 billion. Similar to the overall NIH budget, the FY 2009 budget for the NIAMS is also essentially flat at a proposed total of $509.1 million. At this time, it is estimated that the NIAMS success rate for FY 2009 will be approximately 18.5 percent, similar to that of FY 2008. Funding policies proposed under the President's budget include no inflationary increases for research project grants (RPGs); however, the FY 2009 budget request provides a modest stipend increase of 1 percent for pre- and postdoctoral research fellows to help ensure the pipeline of future investigators is adequate. Dr. Katz noted that more detailed information on the President's budget, including narrative and tabular data, as well as links to the Congressional Justifications for NIH and all of the Institutes, can be found on the NIAMS Web site.

On March 5, 2008, the House Appropriations Subcommittee on Labor, HHS, and Education held its hearing on the FY 2009 budget. Dr. Zerhouni testified at a DHHS panel titled, "Health Issues and Opportunities." He joined his agency counterparts from the Substance Abuse and Mental Health Services Administration, the Agency for Healthcare Research and Quality, and the Centers for Disease Control and Prevention on the combined panel. Dr. Zerhouni's full testimony can be found on the NIH Web site. NIH Institute and Center (IC) Directors submitted written statements for the record (Dr. Katz's statement can be found on the NIAMS Web site).

A February 14, 2008, a house Labor-HHS Subcommittee hearing on "Opportunities Lost and Costs to Society: The Social and Economic Burden of Disease, Injuries, and Disability" was held. NIAMS Council member Dr. James Weinstein, Professor and Chair of the Department of Orthopaedics at Dartmouth-Hitchcock Medical Center, was invited to participate. Dr. Weinstein's statement focused on "informed choices" where patients are empowered to take prominent roles in their own treatment decisions. He used his own research in the NIAMS-funded Spine Patient Outcomes Research Trial (SPORT) as an example of how common treatments for low-back pain may not be the most appropriate from a clinical standpoint in certain situations.

Dr. Zerhouni participated in a May 8, 2008, hearing on "Stem Cell Science: The Foundation for Future Cures." During the hearing, he discussed the potential of stem cell treatments and the importance of additional research.

Dr. Katz announced that after a 13- year effort, the Genetic Information Nondiscrimination Act (GINA) was signed by President Bush on May 21, 2008, as Public Law 110-233. GINA is a federal law that prevents health insurers and employers from discriminating in insurance coverage or employment decisions based on an individual's genetic information, or that of their family members. GINA is intended to allow Americans to take advantage of the benefits of genetic testing and participate in research without fear of losing their health insurance or employment. National Human Genome Research Institute (NHGRI) Director Dr. Francis Collins and Ms. Sharon Terry, President and CEO of the Genetic Alliance and former NIAMS Council member, were instrumental in shaping and pushing this bill through Congress.

Highlights of Selected Recent Scientific Advances

Extramural Research

- This NIAMS-funded study compared surgical versus nonsurgical treatments over a 2-year period for three of the most common causes of low back pain. In this latest paper, NIAMS Council member Dr. James Weinstein of Dartmouth Medical School and colleagues reported that decompression surgery appeared to be superior to nonsurgical treatment in relieving symptoms and improving function in patients who have spinal stenosis without spondylolisthesis (vertebral slippage). Of note, the functional status of patients who received non-surgical interventions also improved somewhat, suggesting that individuals who are reluctant to have surgery to correct spinal stenosis are not subjecting themselves to further damage. In February, the third major paper from the SPORT was published (*N Engl J Med.* 2008 Feb 21;358(8):794-810).

- A number of research groups have been working on magnetic resonance imaging (MRI) methods to detect early and progressive changes in cartilage associated with osteoarthritis. NIAMS grantee Dr. Ravinder Regatte at New York University recently published a paper describing the application of a long-known method of MRI to the quantification of proteoglycans in knee cartilage and, possibly, in intravertebral discs This method, which takes advantage of the inherent chemical properties of tissues rather than relying on a contrast agent, could be safer than other imaging strategies for patients who have reduced kidney function due to age or disease. (*Proc Nat'l Acad Sci U S A.* 2008 Feb 19;105(7):2266-70).

- One of the most important factors in preventing osteoporosis is maximizing bone acquisition during skeletal growth. Work from Dr. Christine Snow at Oregon State and colleagues bone Health recently showed that bone health gains seen in children who participated in a 7-month regimen of "jumping" exercises during regular physical education classes persisted over the long-term. Although the effect diminished with time, children who participated in the jumping protocol continued to have higher bone mineral content than their control-group counterparts, even up to 8 years later (*J Bone Miner Res.* 2007 Dec 11. [Epub ahead of print]; and *Bone.* 2008 Apr;42(4):710-8).

- A team of NIH-funded researchers including Drs. Alexander Robling and Charles Turner recently identified sclerostin as a critical molecular link between mechanical loading and bone formation. This finding opens a new avenue for developing drugs to prevent osteoporotic fractures, because the most popular and convenient therapies for osteoporosis on the market today block bone breakdown, but do little to restore bone that has already been lost. Sclerostin normally inhibits bone formation; however, a simple pharmacologic compound that blocks sclerostin's action would likely lead to bone buildup. Also, sclerostin seems to act specifically in bone, and manipulating its action would be expected to have few effects in other tissues or on processes other than building bone in the skeleton. (*J Biol Chem.* 2008 Feb 29;283(9):5866-75)

- A paper published last month from NIAMS grantees Drs. Caren M. Gundberg and Michael Centrella, both at Yale University School of Medicine, described a novel estrogen-like molecule produced by osteoblasts. The substance triggers several of the biochemical responses induced by estrogen receptor activation. It is chemically distinct from estradiol, and therefore may be safer than the traditional hormone replacement therapies that are prescribed to reduce bone loss in postmenopausal women. (*Proc Nat'l Acad Sci U S A.* 2008 May 13;105(19):7022-7)

- Decades of research on the basic biology of the RyR1 ryanodine receptor and rare diseases associated with RyR1 mutations—such as malignant hyperthermia—have produced exciting data linking RyR1 mutations to an increased susceptibly to heat stroke. Recent findings by Dr. Susan Hamilton of Baylor College of Medicine and colleagues provide insight into the mechanisms underlying muscle damage caused by reactive oxygen and nitrogen species, while also suggesting that heat stroke victims could be treated with the same agents that correct malignant hyperthermia. (*Cell*. 2008 Apr 4;133(1):53-65)

- Drs. Connie Weyand, Jorge Goronzy, and colleagues at Emory University have discovered a new pathway in the interaction of synoviocytes and immune cells in joints of rheumatoid arthritis (RA) patients. In healthy joints, two populations of synoviocytes—fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes—interact with each other. These NIAMS-supported researchers found that lymphocyte function-associated antigen-1 (LFA-1) on T cell surfaces interacts with intercellular adhesion molecule-2 on FLS surfaces, leading to changes, such as increased indicators of FLS activation and numbers of FLS. $CD28^-$ cells, a T cell subset that is more abundant in RA patients, displayed augmented levels of LFA-1 molecules on their surfaces. When cultured with FLS, $CD28^-$ cells stimulated more FLS activation molecules than other T cell subsets. Interestingly, increases in $CD28^-$ cell populations have previously been found to be predictive of more severe RA. Although an initial clinical trial with an agent to block LFA-1 on T cells was unsuccessful in RA patients, this new research suggests the need for further investigation, and the potential for RA therapies that block FLS activation. (*J Immunol.* 2008 Feb 1;180(3):1971-8)

- Treatment with the anti-tumor necrosis factor (anti-TNF) biologic therapy etanercept blocks TNFα, as well as the cytokine, lymphotoxin α. Dr. Ignacio Sanz of Rochester University and colleagues found that etanercept treatment of RA patients had a dramatic effect on B cell development, by reducing the number of regions for B cell-T cell interactions and B cell maturation. These results suggest that etanercept suppresses RA, at least in part, by affecting the functional environment of B cells in lymphoid tissues.(*J. Immunol.* 2008 Jan 15; 180(2):688-92)

- A recent study by Dr. Helen Brunner and colleagues at the University of Cincinnati confirms that children with lupus have more active disease than adults at the time of diagnosis. As well, pediatric lupus patients have more aggressive and severe disease than adult lupus patients, over time. In particular, renal disease in pediatric lupus occurs at a higher frequency, and damage appears to develop more rapidly. (*Arthritis Rheum.* 2008 Feb; 58 (2), 556-562).

- Dr. Howard Chang of Stanford University and colleagues previously demonstrated that fibroblasts from different regions of the body retain a sense of position identity, and they continue to express genes defined by that body location. They predicted that particular *HOX* genes, such as *HOXA13*, may regulate position-dependent features of adult skin via signals from the dermal fibroblasts to the overlying epidermal keratinocytes. Their recent work supports this hypothesis, showing that stable *HOX* gene expression patterns in the adult, and perhaps also positional memory, are maintained by factors which regulate gene expression via activation or inhibition of gene transcription. These studies suggest that position-specific expression of *HOX* genes in fibroblasts may determine site-specific properties of the overlying epidermis through signaling molecules. This new information could have profound importance for tissue engineering, wound healing, cell-based therapies, and for skin diseases that preferentially affect particular parts of the body. (*Genes Dev.* 2008 Feb 1;22(3):303-7).

- Dr. Anne Bowcock at the Washington University in St.Louis and her colleagues performed a genome-wide association study (GWAS) to identify genetic factors involved in susceptibility to psoriasis and psoriatic arthritis. Gene variants in previously-identified regions associated with immune system function were confirmed, such as *PSORS1*, and novel DNA variations were also linked to these diseases. The potential susceptibility candidates include genes known to be involved in immune responses, such as interleukin 2, interleukin 21, and granulysin, and one involved in skin cell differentiation (*PLoS Genetics*, 2008 Mar; 4 (3 el000041 electronic journal).

Intramural Research

- Using the mice as a model system, Dr. Vittorio Sartorelli and colleagues recently found that under low glucose conditions, muscle stem cells failed to differentiate into myocytes (*Dev Cell.* 2008 May pages 14(5):661-73). Furthermore, they defined the molecular pathway by which low glucose inhibits differentiation. This process involves activation of AMP-activated protein kinase which, in turn, stimulates transcription of Nampt, an NAD+ biosynthetic enzyme. Increased NAD+ levels activate SIRT which inhibits myocyte differentiation. This work reveals AMP-activated protein kinase and SIRT as potential targets of muscle wasting disease and provides insights into possible new therapies for type 2 diabetics who suffer from defective blood glucose control.

- Insights into a rare immunodeficiency disorder, Job's syndrome, recently emerged from the laboratory of Dr. John O'Shea, as part of collaboration with scientists from the National Institute of Allergy and Infectious Diseases (NIAID). In a previous study, NIAID researchers found that mutations that cause Job's syndrome map to the STAT3 gene. In this study, Dr. O'Shea and collaborators found that immune cells from Job's patients could not be stimulated to become T_H17 cells, a special type of helper T cell involved in fighting microbial infections. Further, IL17, a cytokine produced by T_H17 cells, was absent in Job's patients. In contrast, healthy controls exhibited T cell differentiation to form T_H17 cells and the presence of IL17. Thus, STAT3 is essential for generation of T_H17 cells. While targeting IL17 is a potential new strategy for fighting inflammatory diseases, this study suggests that a

- Dr. Rocky Tuan and colleagues have developed a new diagnostic assay based on reverse transcriptase-polymerase chain reaction to detect the presence of bacteria in synovial fluid. This test relies on detection of bacterial transcripts that are very rapidly degraded once bacterial cells die; thus detection is limited to live bacteria only. This promising new approach may dramatically reduce the number of patients who needlessly undergo the costly and time-consuming spacer insertion procedure. (*J Bone Joint Surg Am.* 2008 Mar;90(3):602-8).

NIH/NIAMS Activities and Plans for the Future

NIH Activities and Plans

Dr. Katz noted that the NIH Public Access Policy is now in effect for all peer-reviewed articles that arise, in whole or in part, from direct costs funded by the NIH, or from NIH staff, that are accepted for publication on or after April 7, 2008. Requiring scientists to submit final peer-reviewed manuscripts that arise from NIH funds to the digital archive PubMed Central ensures that the public has access to the published results of NIH funded research. Also, as of May 25, 2008, any application, proposal or progress report submitted to the NIH must include the PubMed Central or NIH Manuscript Submission reference number when citing applicable articles that arise from their NIH- funded research.

The NIAMS, National Institute of Biomedical Imaging and Bioengineering, and National Institute of Dental and Craniofacial Research have partnered with the Department of Defense (DoD) on an initiative to speed treatments for wounded soldiers abroad and civilian trauma victims and burn patients here at home. In April, the DoD established the new Armed Forces Institute of Regenerative Medicine (AFIRM). The University-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin. Dr. Fei Wang is the NIAMS' primary liaison in this effort.

The NIH recently announced a new program related to undiagnosed diseases which leverages the opportunities provided by the multidisciplinary and collaborative expertise of NIH researchers and the resources of the NIH Clinical Center. The primary goals of the Undiagnosed Diseases Program, which will be led by Dr. Bill Gahl of the NHGRI, Dr. Steve Groft of the NIH Office of Rare Diseases, and Dr. John Gallin of the NIH Clinical Center, are to: (1) provide hope to patients and physicians who are frustrated by undiagnosed or rare diseases, and (2) perform fundamental research that will help lead to the improved treatment of undiagnosed or rare diseases.

On June 11, 2008, the NIH Research, Condition, and Disease Categorization (RCDC) Program will host a Web-based videocast, or "Webinar" to introduce the RCDC system to the public. Interested parties can view the event—or an archive of it—by visiting the NIH videocast site at http://videocast.nih.gov. It is likely that the Council will be presented with an update on the RCDC Program at a future meeting.

Dr. Katz reminded Council members that the NIH Reform Act of 2006 established a Council of Councils to: (1) advise the NIH Director on matters related to the policies and activities of the NIH Office of Portfolio Analysis and Strategic Initiatives (OPASI), and (2) make recommendations on the conduct and support of trans-NIH research proposals supported by the Common Fund. Council member Dr. Bevra Hahn, Professor in the Department of Medicine at the University of California, Los Angeles School of Medicine, represents the NIAMS Advisory Council on the NIH Council of Councils.

Dr. Katz also announced that the NIH Roadmap initiative known as the Patient-Reported Outcomes Measurement Information System (PROMIS) was recently approved for continued support through the NIH Common Fund. Under the leadership of Dr. Susana Serrate-Sztein, the Project Officer for PROMIS, and Dr. James Witter, the Chief Science Officer for PROMIS, this effort will continue to build and refine a computerized, adaptive testing system for patient-reported outcomes across a wide range of chronic diseases. Dr. Witter was on detail with the NIAMS from the U.S. Food and Drug Administration, and now has a permanent position within the NIAMS' Division of Skin and Rheumatic Diseases. Dr. Katz also acknowledged the contributions of Dr. Louise Rosenbaum and Ms. Anita Linde, both at the NIAMS' Office of Science Policy and Planning, who have been instrumental in organizing the mid-course review for PROMIS and helping to navigate the process for ongoing Roadmap support.

Dr. Katz then discussed a funding opportunity announcement that would facilitate biomedical research on the International Space Station. This activity builds on the Memorandum of Understanding that the NIH signed with NASA last fall and is being spearheaded by the NIAMS as an outgrowth of Dr. Katz's role as the current NIH liaison to NASA, and as a member of the NASA Administrator's Advisory Council. This project is being developed by Dr. Joan McGowan, Dr. Glen Nuckolls and Lieutenant Elijah Weisberg from NIAMS' Division of Musculoskeletal Diseases, and Dr. Jonelle Drugan and Ms. Anita Linde from the NIAMS' Office of Science Policy and Planning.

NIAMS Activities and Plans

Earlier in the week, the NIAMS, in collaboration with the Foundation for the NIH, convened a meeting to present an overview of the largest public-private partnership for Osteoarthritis, the Osteoarthritis Initiative, and related ancillary studies. It has been almost 7 years since the OAI was launched; by the end of FY 2006, baseline data from almost 4,800 OAI participants had been collected. Dr. Katz expressed appreciation for the exceptional leadership of Drs. Joan McGowan and Gayle Lester, and of Council member Dr. Josh Jacobs, who serves on the OAI Steering Committee.

Dr. Katz reported that the National Coalition for Osteoporosis and Related Bone Diseases—composed of the American Society for Bone and Mineral Research, the National Osteoporosis Foundation, the Osteogenesis Imperfecta Foundation, and the Paget Foundation for Paget's Disease of Bone and Related Disorders—is holding a 2-day meeting later this June to develop a coordinated national action plan to promote bone health.

With respect to the Institute's own scientific planning process, in April, the NIAMS held its annual scientific planning retreat. Council members Drs. S. Wright Caughman, Betty Diamond, Ms. Ann Kunkel, and Larry Raisz attended; Council members were provided with an overview of the retreat later in this meeting. In addition, a February roundtable meeting was convened to discuss ways in which approaches to GWAS can be applied to the NIAMS mission areas. A summary of this meeting is on the Institute's Web site and Council members were briefed during this meeting. In March, NIAMS representatives met with members of the rheumatology community, including representatives of the American College of Rheumatology (ACR), the ACR Research and Education Foundation, and the Arthritis Foundation, to explore career path issues for rheumatology researchers.

In terms of information dissemination efforts, the NIAMS has developed an updated list of registries that are currently supported by the Institute to encourage the utilization of existing research resources by investigators. These registries provide a wealth of information to researchers about a variety of diseases within the Institute's mission. The list is available on the NIAMS Web site; the registries can also be found by searching ClincialTrials.gov.

Council members were provided with copies of two recent media pieces featuring NIAMS staff and programs:

- Dr. Gayle Lester is featured in the summer 2008 issue of *Medizine's Healthy Living*, the largest consumer health magazine in the country with distribution in more than 30 pharmacy chains (70,000+ actual stores) and physician offices nationwide. The article, entitled "Dancing Feet: How to Head Off or Deal With Osteoarthritis," provides strategies for keeping joints healthy and coping with arthritis-related pain.

- The NIAMS was featured in the March 2008 issue of *U.S. Medicine*, a publication with a global readership of approximately 43,000 Federal health professionals. The article explores Federal initiatives in rheumatoid arthritis research.

Council members also were provided copies of a new, easy-to-use guide to assist patients and their families with getting the health information they need. The NIAMS partnered with the National Institute on Aging and other DHHS agencies to develop this brochure, based on a national needs assessment with community health partners.

Discussion

Council member Dr. Cliff Rosen, Director of Translational Research at Maine Medical Center, asked about the budget process and whether, in an election year, it is more likely that the budget process will be facilitated more easily or is more likely to extend into the following year. Dr. Katz indicated that a lead staffer on Capitol Hill has predicted that the NIH will not have a budget by the start of the next fiscal year; there are only about 7 weeks of activity remaining in Congress this year, and it is likely that there will not be a new budget until the new administration arrives. Dr. Katz reminded the Council that there is a large amount of support for the NIH and health-related research on the Hill.

Dr. Betty Diamond, a member of the Council and Chief of the Laboratory of Autoimmune Diseases at Feinstein Institute of Medical Research, noted that there is a significant concern in the extramural community that the current budget environment may continue for many years. She asked whether there is an NIH-wide process in place to look at ways to consider what the size of the scientific enterprise should be and what the scope of NIH training efforts should be. She also noted that researchers are leaving the world of extramural investigative science because of an enormous sense of demoralization associated with a lack of funding. Dr. Katz responded that the NIAMS and other ICs grapple with these issues on a regular basis. At the NIH level, the importance of sustaining new investigators is a central theme, as is looking for cost savings wherever possible in the face of stagnant budgets and increasing information technology costs.

V. HIGHLIGHTS OF THE COUNCIL OF COUNCILS MARCH 31-APRIL 1, 2008 MEETING

Council member Dr. Bevra Hahn, who represents the NIAMS Advisory Council on the NIH Council of Councils, provided a brief summary of the March 31-April 1, 2008, meeting of the Council of Councils. Dr. Hahn reminded NIAMS Advisory Council members that the NIH Council of Councils was formed to advise the NIH Director and provide oversight, particularly in terms of matters relating to use of the Common Fund. She noted that remarks by Dr. Zerhouni at the March 31-April 1 meeting stressed the high importance of open, transparent, and bi-directional communication between the Council of Councils and individual IC advisory councils. At the meeting, Dr. Zerhouni also emphasized that the Council of Councils is challenged with assessing where the frontiers are and promoting high-risk ideas. In addition, he noted the impact and profile that the Council of Councils is expected to have and the amount of interest in its activities. Dr. Hahn reported that the Council of Councils has established subcommittees aligned with the three Divisions of the Office of Portfolio Analysis and Strategic Initiatives (OPASI): (1) the Division of Resource Development and Analysis (DRDA), (2) the Division of Strategic Coordination (DSC; Dr. Hahn is a member of this subcommittee), and (3) the Division of Evaluation and Systematic Assessment (DESA).

Dr. Hahn discussed highlights from some of the presentations at the March 31-April 1 meeting of the Council of Councils.

- **OPASI Reports.** Through working groups and subcommittees, the Council of Councils will provide input on the generation and vetting of trans-NIH initiatives, and review and approve FY 2010 concepts at its November 20-21, 2008, meeting for submittal to ICs.

- **Interdisciplinary Research.** The context, background, and challenges to interdisciplinary research, which does not necessarily equate with team science, were discussed.

- **Molecular Libraries Roadmap Initiative.** This project is a marriage of chemistry and biology and represents the largest Roadmap initiative. The project is almost at the end of its pilot phase and is undergoing rigorous peer review.

- **New Concepts and Current Roadmap Topics.** This was the subject of a report of the February 29, 2008, IC Retreat regarding Common Fund programs for FY 2009 and FY 2010.

- **Public-Private Partnerships and Foundation for NIH.** This discussion focused on public-private partnerships leveraging NIH resources to achieve synergy. The Foundation for NIH expands the number of funded NIH grants through parallel grants or additional funds from other agencies. Dr. Katz noted that the Osteoarthritis Initiative was the first of these projects.
- **Working Group and Subcommittee Reports.** Brief reports were submitted on the two working groups reviewing the Research, Condition, and Disease Categorization (RCDC) System and the three Council of Councils subcommittees.

Dr. Hahn reported that the next Council of Councils meeting will be held November 20-21, 2008, on the NIH Campus. That meeting is expected to focus on: (1) a working group report on the science of science management, (2) a report from the NIH Obesity Research Task Force, (3) the role of OPASI in trans-NIH obesity and nutrition research, (4) the burden of disease in obesity and nutrition, (5) the microbiome, and (6) approval of trans-NIH Roadmap initiative concepts.

Discussion

Dr. Katz noted that at the September 2008 Council meeting, it may be beneficial to have OPASI Deputy Director Dr. Alan Krensky, or a representative from his office, brief the NIAMS Advisory Council on the Roadmap initiatives. Dr. Katz then thanked Dr. Hahn for representing the NIAMS Advisory Council on the NIH Council of Councils.

VI. REPORT ON THE EP SCIENTIFIC RETREAT

Dr. Katz introduced this session, noting that the NIAMS Extramural Program Scientific Retreat is an opportunity to address issues across ICs and the NIH as a whole. The following paragraphs summarize presentations to the Council on topics discussed at the Retreat

Gene Therapy for Arthritis and Musculoskeletal and Skin Diseases

Council member Dr. S. Wright Caughman, Professor in the Department of Dermatology at Emory University School of Medicine, noted that the overarching question guiding discussion during this part of the Retreat was: What are the gaps and opportunities, and what can the NIAMS do to advance the application of gene therapy (GT) to diseases and disorders within its mission? Dr. Caughman described the advantages of GT, which include: (1) the potential replacement or correction of single-gene defects; (2) up- or down-regulation of pathways involved in pathology or natural repair mechanisms; and (3) synthesis, processing, and delivery of GT products at the disease site.

Dr. Caughman reported that GT studies for arthritis and musculoskeletal, and the skin diseases are ongoing within the NIAMS or supported by the NIAMS in the areas of wound healing, genodermatoses, rheumatoid arthritis, osteoarthritis, and muscular dystrophies. It was

recognized at the Retreat that there are substantial knowledge gaps, particularly in the areas of: (1) vector biology, (2) immune response to vectors and transgenes, (3) regulation of transgene expression and silencing, and (4) stem cell biology. Discussion at the Retreat emphasized the importance of interdisciplinary collaborations among vector and stem cell biologists, immunologists, tissue engineers, transplantation biologists, disease-specific physicians, and regulatory approval experts.

Infrastructure and resource needs to support the community also were identified. These include central services and support for preclinical testing and vector production, as well as activities (meetings, funding opportunities) to facilitate exchange of information and formation of interdisciplinary collaborations. Regulatory and review issues also were addressed (e.g., harmonization among regulatory organizations) and the importance of multidisciplinary peer review, including GT expertise, for the evaluation of GT applications.

Discussion

Dr. Katz commented that the general consensus at the Retreat was that although GT has gone through some rough phases, there are important opportunities that must be addressed to, despite the challenges in this field. Council member Dr. Kathleen Green, the Joseph L. Mayberry Professor in the Department of Pathology/Cancer Center at Northwestern University Medical School, asked about the level of effort required for silencing approaches versus transgene and other traditional approaches. She also asked how much of the NIAMS portfolio is dedicated to Small Business Innovation Research (SBIR) and Small Business Technology Transfer Program-related GT approaches. Dr. Caughman noted that there is evidence that complete correction of some genetic defects isn't necessary; partial correction in some cases can lead to sub-clinical disease. He added that there also was discussion on the recent work in generating potential stem cells produced from skin. It may be possible to alter stem cells to express genes that were defective. Dr. Diamond also asked about the effort being put in to examining off-target effects, interferon responses, and similar issues. Dr. Carl Baker of the Division NIAMS' Skin and Rheumatic Diseases agreed that these are important areas, but they are not supported by the Institute's SBIR Program. Dr. Katz reminded Council members that consideration is being given to targeting a portion of SBIR funding to specific areas of study; this topic may qualify as one of those areas. An update on the SBIR Program will be given at the Council's September 2008 meeting.

Chronic Pain

Council member Dr. Betty Diamond explained the overarching question guiding discussion at the Retreat as it related to the topic of chronic pain: How can the NIAMS contribute toward understanding chronic pain and developing treatment options for patients who suffer from chronic musculoskeletal pain? Dr. Diamond added that another, overarching scientific question: When pain ceases to be a symptom and becomes a disease, what is the physiology of that transition, what is the physiology of the state of pain, and how many physiologies are there?

Key discussion points focused on the types of pain, neuroplasticity and pain, and heterogeneity of pain syndromes. Dr. Diamond reminded Council members that "all pain is not the same" and

that there are four types of pain: (1) nociceptive, protective pain (generated by the presence of tissue-damaging stimuli and responds to NSAIDs and opioids); (2) neuropathic pain (caused by damage or entrapment of peripheral nerves and responds to neuroactive compounds and traditional analgesics); (3) inflammatory pain (caused by tissue injury); and (4) dysfunctional, non-nociceptive (central) pain (which occurs without obvious signs of tissue damage). Dr. Diamond noted that inflammatory pain and non-nociceptive pain are associated with allodynia, the perception of pain in response to a benign stimulus, as well as hyperalgesia: heightened sensitivity to noxious stimuli.

A major topic of consideration at the Retreat was interactions among the peripheral and central nervous systems and the inflammatory system. Dr. Diamond explained that patients with chronic pain conditions undergo neurobiological, psychological, and cognitive and behavioral changes that dramatically affect symptoms and functioning. Also discussed at the Retreat were reversible and permanent biochemical and anatomic changes that cause or are caused by pain. These include mechanisms underlying allodynia and hyperalgesia, as well as the transition from pain as a symptom of a disease to a chronic condition that can be prevented, treated, or cured. Dr. Diamond reported that there also was discussion on the heterogeneity of pain syndromes, with a focus on genetic risk factors, mechanisms by which chronic pain develops, and variations in phenotypic manifestations.

There also was a discussion of genetic risks that predispose individuals to move from acute pain to chronic pain, the environmental factors that might contribute to this transition, the biochemistry and relationship of acute pain to chronic pain, and the therapeutic modalities that need to be considered beyond NSAIDs and analgesics. There was an overall consensus that this is an important area, and that better tools are needed to evaluate and differentiate between different types of pain. Dr. Diamond noted that this is clearly a very interdisciplinary problem, and studies of pain should be married to studies of different diseases connected to pain syndromes (e.g., arthritic conditions).

Discussion

Dr. Katz commented that NIH wide, there is a significant concern, that although a lot of money is being invested in pain research, the challenge is bringing new ideas to the table. In response to a question about the robustness of animal models used to study pain, Dr. Diamond commented that there was an overall sense at the Retreat that more of these types of models are needed. There is a concern that in animal models, some of the downstream effects of chronic pain (e.g., cognitive function, sense of well-being, fatigue) have not been and perhaps cannot be effectively addressed in animal models. In some ways, this is a field that is in its infancy but gaining momentum as new tools and paradigms for thinking about pain are developed.

Centers Management

Dr. Diamond noted that the overarching question guiding discussions focused on the issue of centers management was: How can the NIAMS manage its centers awards to enhance success, productivity, cost savings, and efficiency? The purposes of the NIAMS centers grants are to: (1) provide funding for infrastructure, translational, and clinical research projects that are not easily

supported through investigator-initiated funding mechanisms; and (2) establish initiatives to induce the development of projects in areas that the NIAMS is not receiving in investigator-initiated proposals. Types of NIAMS centers include:

- **Research Core Centers** (P30: infrastructure support for research in an NIAMS mission area)
- **Centers of Research Translation** (P50: disease-specific, multi-project awards in translational research).

- **Multidisciplinary Clinical Research Centers** (P60: generally outcomes or epidemiology studies).

Retreat discussion focused on the evaluation of centers. Dr. Diamond explained that, instead of publication citations, the evaluation criterion is whether the effort is moving the field forward. Retreat participants also discussed centers communications and interactions. It was noted that face-to-face meetings and regular teleconferences are valuable, and that institutional distribution of pilot grants helps new investigators and fosters collaborations. In terms of the management of collaborative activities at NIAMS centers, Dr. Diamond reported that consortia develop around common scientific interests, shared resources, and funding. Investigators and institutions sometimes balance priorities between individual interests and collective efforts. Dr. Diamond noted that there was a sense at the Retreat that these centers need more intellectual interaction with NIAMS staff, and that these interactions can lead to value-added benefits to the centers. The advisory committees for NIAMS centers are external advisory boards that provide critical guidance to centers and NIH science officers. Decision-making power has been found to enhance the engagement and effectiveness of advisory board members.

Discussion

Dr. Katz noted that Retreat participants were influenced by the active role that Dr. Glen Nuckolls of the NIAMS Division of Musculoskeletal Disease has played in terms of the muscular dystrophy centers, which is distinct from the role that other programs have played with regard to the centers. Council member H. Lee Sweeney, the William Maul Measey Professor and Chair of the Department of Physiology at the University of Pennsylvania School of Medicine, noted that his center is a U54, defined as a cooperative center, and is mandated to have the interactions described by Dr. Diamond. These interactions have supported by the U54 mechanism added value and made it a true community resource; Dr. Sweeney indicated that these interactions are effective and beneficial to the point where it could serve as a model for other centers. Dr. Katz noted that the challenge is that there is far more commonality associated with groups at the cooperative centers than in others.

Dr. Caughman agreed that face-to-face meetings onsite provide connectivity between the investigators and institutes, and also reinforces the institutional commitment to the center. He explained that successful grants come in with substantial institutional commitment, and the presence of NIH involvement in the monitoring and governance of that grant reinforces the oversight of continued institutional commitment. Dr. Sweeney noted that even in cases where there aren't necessarily areas of common scientific interest, these types of meetings and

interactions can be valuable to discuss common processes, limitations, and other issues. Dr. Nuckolls added that it takes time to establish these valuable collaborations and interactions between different centers.

Ancillary Studies to Large Clinical Projects

Council member Dr. Larry Raisz, Director of the University of Connecticut Center for Osteoporosis within the University of Connecticut Health Center, noted that the overarching question guiding discussion in this area was: Should the NIAMS consider any new policies or mechanisms to enhance or facilitate the use of ancillary studies in its mission areas? Key discussion points at the Retreat included review considerations, which will vary with proposed studies, and guidance for investigators designing ancillary studies.

Retreat participants reviewed a number of points of consideration,. For example, with regard to the NIH Center for Scientific Review (CSR) process, the approximately 9 months (or more) period between application submission and funding is incompatible with ancillary studies that must start concurrently with the parent study. Expedited review to encourage ancillary studies was discussed, with two examples offered (the National Institute of Allergy and Infectious Diseases' [NIAID] Hyperaccelerated Award/Mechanisms in Immunomodulation Trials [R01], RFA-AI-05-028; and the National Heart, Lung and Blood Institute's Ancillary Studies to Clinical Trials [R01], RFA-HL-07-009). Retreat participants also discussed the fact that applications that are not as time-sensitive as those for ancillary studies could be reviewed through the standard CSR system. Examples include post hoc studies and those that do not require additional baseline measurements.

Dr. Raisz commented that many investigators are not aware of the possibility of conducting ancillary studies, and that the Institute could facilitate promoting this fact more proactively to its researchers. The need to provide guidance to investigators of ancillary studies was discussed at length during this session of the retreat. Dr. Raisz explained that issues to be negotiated with the parent study before starting an ancillary study include: (1) data access and processing, (2) sample storage and sharing, (3) publication and authorship, and (4) payment to parent studies for staff time and data collection. In terms of recruitment, investigators need to understand that participation has to be voluntary, with additional consent requirements. Investigators also should be aware that they may not recruit the desired subset of patients. Dr. Raisz noted that before applying for funding (even under existing mechanisms), investigators should obtain written agreements from parent trial sponsors and investigators, as well as approvals from the Institutional Review Board, steering committee, and Data Safety and Monitoring Board.

Discussion

Dr. Katz noted that a mechanism similar to NIAID's Hyperaccelerated Award/Mechanisms in Immunomodulation Trials R01 is being considered by the NIAMS. With the static budget situation, priority setting becomes even more critical. He noted that it is unfortunate that when there is a large clinical study and there can be mechanistic studies added to it at a minimal cost, budgetary constraints often prevent the conduct of these additional studies.

NIAMS Training Program

Dr. Caughman noted that this discussion at the Retreat was a follow-up to a September 2007, NIAMS training evaluation report that considered the T32, F32, and K award NIAMS training grant mechanisms, with a primary focus on issues surrounding the T32 mechanism. Key discussion points addressed at the Retreat included: (1) options for encouraging trainees to obtain innovative training experiences; (2) how to address challenges in the review of T32 and K applications; (3) the effectiveness of the T32 in feeding and maintaining the trainee pipeline; and (4) whether the NIAMS should shift its emphasis from the institutionally awarded training grants, such as the T32, to individual awards.

Dr. Caughman provided an overview of the training program discussion highlights. For example, there were varying points of view on whether the NIAMS T32 program has been successful. Some Retreat participants felt that the Institute should not shift emphasis away from the T32 because of its vital role in feeding the research investigator pipeline. They commented that the benefits to departments go beyond providing a way to pay fellows' salaries. Other participants, however, felt that too many T32 slots are occupied by trainees who have no intention of pursuing research and that the NIAMS should shift its emphasis to other mechanisms. It was noted that mechanisms that could fill in for the T32 include K12 programs within CTSAs.

Dr. Caughman reviewed other themes that arose during the retreat discussion on this topic. If the NIAMS decides to divert funding away from the T32 mechanism, there was consensus that it should consider increasing its investment in K awards rather than the F32. Any reduction in the T32 should be implemented in terms of the number of slots per program, rather than a reduction in the total number of programs. Additional evaluation of the training programs (particularly the T32) would likely be valuable. One way that the NIH could help maintain the trainee pipeline is to address difficulties in recruiting scientists from abroad. These include the amount of time required for foreign trainees to obtain a green card.

Discussion

Dr. Joshua Jacobs, a member of the Council and an orthopaedic surgeon at Rush University Medical Center, commented on the recommendation about supplanting the F32s with K12 awards, noting that the K12 awards existed before the CTSAs were established. He asked if there was any information available regarding the success rate of the K 12 awards. Dr. Katz explained that in prior years, there were very few experts in NIAMS disciplines who were awarded K12s, because they have been traditionally distributed by the deans of medical schools, who often selected other disciplines for these awards. He added that there really is no track record in terms of the NIAMS giving K12 awards to institutions that, in turn, select the awardees. Dr. Katz also noted that the landscape has changed in that there are now researchers participating in CTSAs who have received K12 awards and who work in fields related to the NIAMS mission areas.

Dr. Kathleen Green discussed the difference between M.D./Ph.D. programs versus "pure Ph.D." training. She commented that the NIAMS, in its training programs, appears to place a lot of

emphasis on physician scientists, but at the extramural institutional level, there is a bigger pipeline for postdoctoral in other areas such as the NCI. Many areas of interest to the NIAMS get funneled into cancer and other areas of research because of the opportunities for NCI-supported cancer research training postdoctoral funding. Which may have the unintended consequence of having some of the NIAMS' best potential researchers move into other discipline areas?

Dr. Diamond commented that one of the issues with the T32s is to understand what constitutes "success" (e.g., Ph.D.s who moves to independent funding). This issue needs to be analyzed in greater detail to help improve outcomes. Dr. Katz agreed, noting that this was a clear limitation of the 2007 report. Dr. Jacobs added that using independent R01 funding as a metric may be more appropriate for a Ph.D. researcher than an M.D. researcher. Dr. Katz noted that, in bone biology, there are very few training grants yet it is an active and growing field—identifying where these experts are trained is another issue.

Dr. Hahn asked what some other measures of successful outcomes would be. Dr. Katz responded that industry leadership could be an example. Dr. Hahn asked if a full-time academic appointment would be an appropriate measure of success as well. Dr. Katz indicated that such an appointment, in addition to intellectual knowledge, may be an appropriate measure. Dr. Caughman added that there is a need to broaden the criteria for success and to find ways to encourage T32 applicants to be ecumenical and innovative in the utilization of those trainee slots so to bring more science into a discipline and expand the field.

VII. TRANSLATIONAL RESEARCH – FOCUS ON CORT AND CTSA

Dr. Arnett discussed how a CTSA can advance and add value to the NIAMS research programs, using the University of Texas Health Sciences Center's (UTHSC) Center of Research Translation (CORT) in scleroderma as an example. Dr. Arnett began by providing a brief overview of the UTHSC CTSA and its components. The CTSA includes investigators and educators from all five of the degree-granting schools within the UTHSC. The UTHSC Center for Clinical Translational Science (CCTS) also has major partners with the MD Anderson Cancer Center, as well as the largest hospital system in Houston. Dr. Arnett also reviewed the components of the CTSA (e.g., Administration, Biomedical Informatics, Ethics and Advisory, Community Engagement, etc.).

Each CCTSA is configured into a department, center, or institute, depending on the home institution. The UTHSC CTSA home includes "one-stop shopping" for research projects, where both investigators and trainees can go for assistance with: (1) administrative issues; (2) biostatistics, epidemiology, and research design; (3) regulatory issues (such as IRBs, conflict of interest, etc.); and (4) ethics and advocacy issues. The CCTSA also includes offices and conference/meeting rooms for staff, trainees, and mentors.

For training, the CTSAs include both K12 and T32 awards, as well as K32 awards. K12 scholars receive 75 percent protected time plus $15,000 for ancillary expenses. The UTHSC CCTSA has developed a very active "K Club" to facilitate peer mentoring. It also includes T32 trainees

(M.S. and/or Ph.D. trainees), as well as a K30 clinical research curriculum. Dr. Katz asked if any K30 awardees at the Center were studying the areas of skin or bone biology. Dr. Arnett replied that those areas currently are not represented in that group. He noted that the Center also has established a Masters in Clinical Research program, as well as M.D./Ph.D. training. Dr. Arnett provided CORT examples of trainees in rheumatic and skin diseases research, including rheumatologists, a dermatologist, and a pulmonologist.

Dr. Arnett explained that the UTHSC CTSA has helped to simplify regulatory hurdles. For example, the Center has a merged, electronic application for the IRB, research conflicts of interest, hospital application, and scientific review. The Center also provides a expedited application process (e.g., IRB, etc.) between UTHSC and MD Anderson Cancer Center for research administration projects.

Dr. Arnett noted that the CCTS core laboratories (which provide at-cost expedited services to CCTS members) have been very helpful. These core laboratories provide expertise and facilities for genotyping and sequencing, microarray (expression and single nucleotide ploymorphism chips), reverse transcriptase-polymerase chain reaction, proteomics, immune monitoring, high-throughput drug screening, and magnetic resonance imaging. Dr. Arnett commented that CCTS UTHSC CTSA is a unique engine of innovation, or think tank, where prominent basic, clinical and translational scientists convene at an annual retreat and serve as mentors. At the first retreat, various focus groups were formed (e.g., in the areas of inflammation, perinatology and women's health, single-gene disorders, and musculoskeletal disorders). At this year's retreat, it was decided that seed grants in the amount of $125,000 would be awarded to each of two focus groups to develop multidisciplinary P50 and PO1 applications.

In terms of informatics linked to the CTSA, Dr. Arnett noted that the i2B2 system (clinical data mining from de-identified patient records) has been adopted. Other informatics systems described by Dr. Arnett include eConsent (electronic consent forms), Geneologics™ (genetic and proteomic core lab management), and CCTS Biobank (1,800 normal Mexican-American controls that can be used across the CTSA and with collaborators).

Dr. Arnett described the CTSA Consortium, noting that there are now 38 Centers (at the program's onset, 12 were established). A strategic plan for the consortium which will ultimately have 60 CTSAs, this is currently is under development. The plan will address a number of Consortium features, such as shared data management systems, a national resources inventory, best practices in clinical research guidelines, clinical trials networks, biorepositories, and identity management plans. IRB simplification may be considered, along with other issues.

Discussion

The CTSA at University of Michigan Dr. Clauw noted that his CTSA has a significant number of K12 awardees engaged in musculoskeletal research and described three of their research projects. He explained that they have been successful in utilizing the K12 mechanism to pursue research areas of interest to the NIAMS. There are required programs but there is latitude as to how these programs can be structured. Dr. Clauw described a 2-year postdoctoral program that takes 10 individuals who have two to ten basic sciences and provides a clinical immersion

experience to equip them as translational researchers (i.e., providing the clinical element of translational research).

Dr. Anthony Hayward, Director of the Division of Clinical Research Resources at the National Center for Research Resources (NCRR) and head of the CTSA program, explained that the aim of the CTSA program is to make resources available to investigators. He reminded the Council that one doesn't necessarily have to have an NIAMS awardee as the PI for CTSA awards. He estimated that about 4 percent of the awards the NIAMS makes extramurally go to institutions that receive support through CTSAs. He expressed hope that NIAMS clinical investigators will request more support from CTSAs.

Dr. Katz explained an early concept for CTSAs was a home for clinical research in an institution or multi-institutional collaboration. Another concept was CTSAs facilitating research in rare diseases and in areas such as Rheumatic Diseases in children. Another idea was to have the CTSA program interdigitate with the Institutes to facilitate, accelerate, expedite, simplify, and harmonize clinical research challenges. Dr. Arnett noted that these activities already are occurring, and used the example of a scleroderma program being supported by the UTHSC CTSA. Dr. Katz asked if other programs will interact with this program in scleroderma. Dr. Arnett expressed hope that this will be the case. The scleroderma program includes a biorepository, which could be shared with any of the other CTSAs as well as with any investigator undertaking a peer-reviewed project.

Dr. Clauw agreed with Dr. Arnett that the CTSAs add value for researchers, even though the program has not been in existence for very long. Researchers who take advantage of the CTSAs receive benefits such as services and support.

Dr. Katz noted that a CTSA will be more internally focused for the first year or two of its existence. He asked when outreach to other programs becomes a priority. Dr. Arnett commented that the UTHSC CTSA's Informatics Steering Committee is one of the busiest and most active in the CTSA program, and outreach is a primary effort. Dr. Hayward emphasized that sharing and outreach will be key to the CTSA program success and described the Star Bright software suite, which provides investigators with recommendations on regulatory support, participant recruitment, data analysis, etc. The CTSA Web site (www.ctsaweb.org) has more information on this software.

Dr. Diamond noted that, if the CTSA Consortium is going to reach its full potential, attention must be given to being include investigators outside of the CTSAs and to disease-related organizations in terms of outreach and patient education programs. As these shared activities develop, it will be important there be ever enlarging concentric circles, and that they not stay within one single program. Dr. Jacobs asked about the impact a change in NIH leadership with a new administration in January, 2009 might have on this particular Roadmap initiative. Dr. Katz responded it would not alter this program, as it is mandated by legislation. The NIH has made a commitment to the CTSA program, and has set funds aside for it. Dr. Hayward agreed, noting that he and his colleagues see the CTSA program as one that fulfills the needs of investigators and will likely continue receiving support from across the NIH.

VIII. REPORT ON THE NIAMS ROUNDTABLE DISCUSSION ON GENOME-WIDE ASSOCIATION STUDIES (GWAS)

Dr. William Sharrock, of the NIAMS' Musculoskeletal Diseases Division, explained that this discussion was organized because this field has advanced quickly from it and much can be learned from it about the relationship between certain diseases and genetic variations. A guiding question was how the various research communities that the NIAMS supports can make the best use of this approach, and what resources it will take. Dr. Sharrock and NIH roundtable participants who represented rheumatoid disorders, skin, osteoporosis, and osteoarthritis research communities.

Some of the roundtable discussants have already made significant progress in the area of GWAS. Dr. Sharrock noted that GWAS have proven to be valuable in understanding a variety of diseases. These studies require large samples and large investments in genotyping. Consortium-approach is often necessary. GWAS were supported initially through trans-NIH initiatives, but they were currently moving to individual IC portfolios. Some of these projects may need special oversight or targeted initiatives by the NIAMS to facilitate collaboration and ensure optimal use of resources (e.g., data, samples, control populations, bioinformatics support.). Dr. Sharrock emphasized the importance of assessing the GWAS-related needs of the research communities working in the NIAMS mission areas.

Dr. Rosen, who was the roundtable co-chair with Dr. Sharrock, said that this forum presented a unique opportunity to bring together experts within the NIAMS sphere who are studying different disorders but who share common issues related to the study of genetic polymorphisms and their relationship to disease. The roundtable discussant agreed that:

- Different communities are at different stages of addressing the potential and challenges of GWAS.

- Different diseases require different approaches (rare vs. common, case/control vs. quantitative trait), and phenotype definition is critical to study design. Validation of large samples by other large cohorts requires a consistent approach to phenotyping.

- Some productive consortia have formed, within the United States and abroad without overt direction by the NIH.

- Some projects may benefit from a higher level of IC involvement, special funding mechanisms, or requirements of study design and data consistency.

- Crucial followup studies—including replication, fine mapping, and extensive sequencing—may require targeted support.

Dr. Rosen commented that this work is multidisciplinary in nature, and the real challenge for GWAS in 2008 is understanding what loci of interest mean and how they can be used. A study recently published in the *New England Journal of Medicine,* titled "Multiple Genetic Loci for

Bone Mineral Density and Fractures." Investigators on this large GWAS used approximately 5,800 Icelandic individuals to identify five loci that contributed to both bone density and fracture risk. Through the development of a consortium the researchers have two additional cohorts to validate these data. Dr. Rosen noted that these five loci combined only accounted for 1.5 percent of the variation in bone density, suggesting that there is significant challenge ahead in complex diseases such as osteoporosis. Dr. Rosen summarized that the roundtable discussion was very insightful. He noted that it is not clear whether there is a GWAS "roadmap" yet, as this area is very heterogeneous across diseases and across disciplines.

Discussion

Dr. Katz asked how the NIAMS should proceed with regard to GWAS. He noted that NIH new data sharing policies are moving researchers more rapidly toward forming consortia. Many prominent, peer-reviewed journals, such as the *New England Journal of* Medicine, almost require a validation cohort with the original cohort. Dr. Daniel Kastner, NIAMS Clinical Director and Chief of the NIAMS Genetics and Genomics Branch, explained that the results of GWAS probably do not provide all of the insight into diagnosis that many would hope. However, they identify specific pathways that might be important in the pathogenesis of disease and suggest therapeutic targets that may be amenable to the treatment of patients.

Dr. Rosen noted that there are probably areas where the NIAMS could be more active with respect to GWAS such as facilitating meetings of experts to address a certain problem (e.g., what resources are available to pursue GWAS in a specific complex disease). Dr. Katz noted that NIAMS brought together leading psoriasis investigators from several academic centers. The groups that came together for this meeting were very competitive with each other, but worked through a number of issues to have enough samples to conduct followup studies and move the field forward. Dr. Katz emphasized the importance of these types of interactions occurring in other areas of interest to the Institute, as well as the importance of "playing together in a sandbox" rather than working in isolation.

IX. UPDATE ON 2007-2008 PEER REVIEW SELF STUDY

Dr. Lawrence Tabak, Director of the National Institute of Dental and Craniofacial Research, noted that first-rate peer review is a cornerstone of the NIH. In science and recent funding trends the increased breadth and complexity, creates challenges to NIH's peer review system. In response, the NIH developed a plan to evaluate and enhance peer review at the NIH. The NIH peer review system has been charged by Dr. Zerhouni to "fund the best science, by the best scientists, with the least administrative burden." Dr. Tabak noted that this charge needs to be put within the context of factors such as scientific quality, public health impact, IC mission, and the existing NIH portfolio.

Dr. Tabak summarized the process used in developing the implementation plan for enhancing peer review at the NIH. The initial phase of this work culminated in a draft recommendation report after obtaining substantial input from within and outside of the NIH, released on February 28, 2008. A draft implementation plan was completed on April 16, 2008, and is now being

vetted throughout the NIH (prior to his presentation, Dr. Tabak presented the draft plan to the Advisory Committee to the Director). In developing the plan, Dr. Tabak explained that efforts were guided by several principles, including: (1) do no harm, (2) continue to maximize the freedom of scientists to explore, and (3) focus on the changes that are most likely to add significant value at a reasonable cost/benefit ratio. As a result of the iterations, feedback, and analyses associated with developing the draft implementation plan, four core priorities emerged:

Engage the Best Reviewers

Dr. Tabak commented that the excellence of NIH's peer review system is fundamentally correlated to its ability to recruit and retain the most accomplished, broad-thinking, and creative scientists to serve on study sections. He presented data showing the academic rank of all CSR reviewers. In the last 10 years, more than half of CSR reviewers hold the rank of Professor. Dr. Tabak then presented six goals associated with the priority of engaging the best reviewers:

- Increase the flexibility of service to better accommodate reviewers.
  - Spread the 12-session reviewer commitment over 4-6 years.
    - Allow duty-sharing by colleagues, as appropriate.
  - Expand the use of reviewer's flexible funding application submission deadlines.
  - Pilot and evaluate new forms of high-bandwidth electronic review.

- Recruit additional accomplished reviewers to serve on study sections.
  - Enhance recruitment strategies to attract a greater number of accomplished extramural and intramural investigators to serve as reviewers.
  - Establish a policy that certain classes of NIH grant awards would include a service expectation for PIs, including:
    - Honorific awards: Merit/Javits, Pioneer
    - Grants where the PI is named as PI on three or more additional R01 equivalents,
    - Grant renewals with more than $500,000 in direct costs.

- Acknowledge the efforts of all reviewers more formally.

- Make the review experience intellectually more rewarding.
  - Focus the discussion on impact and innovation/originality of proposals.
  - Ranking proposals at the meeting's conclusion will provide feedback to the study section members.
  - Study sections will be engaged directly in the piloting of many of the peer review changes.

- Compensate the time and effort required for outstanding and sustained service for reviewers who serve for a minimum of 18 full study section meetings as chartered members or equivalent service.
  - Individuals may apply for an administrative supplement of up to $250,000 (total compensation).
  - Individuals may request that they be considered for Merit/Javits awards on a competitive basis.

- Enhance review quality by providing additional training and mentoring to all study section chairs, reviewers, and Scientific Review Officers.
  - Develop an NIH-wide, standardized core curriculum based on best practices, augmented by IC- and study section-specific additions.

Improve the Quality and Transparency of Reviews

Dr. Tabak emphasized that peer review must consistently identify an application's relative merit, potential for scientific and/or public health impact, and feasibility. He explained that previous work has found that the reliability of individual rating scales is a monotonically increasing function of the number of steps; seven scale steps has been found to provide the appropriate balance between scale reliability and discriminative demand on the respondent. Today, the NIH peer review system uses an unjustifiably high 41 scale steps, but will be moving towards seven in the future. Dr. Tabak presented the following three goals associated with improving the quality and transparency of reviews:

- Modify the rating system to focus on specific review criteria, with less emphasis on methodological details and more emphasis on potential scientific impact.
  - Assigned reviewers will provide individual scores for each of the five review criteria (1-7) and a preliminary global score.
    - Five specific review criteria: impact, investigator(s), innovation/originality, project plan /feasibility, and environment.
  - For applications that are not streamlined:
    - All study section members, based on a discussion of each criterion, will provide a global score (1-7).
    - After initial scoring, all proposals within relevant categories will be discussed as a group and ranked in some manner.
    - Ranking at the conclusion of the meeting allows for "recalibration" of global scores.
  - To provide all applicants with specific feedback, applications that are streamlined will receive five scores—one for each criterion, representing the average from all reviewers.

- Restructure the summary statement to align with the explicit rating criteria.
  - Develop and use a summary statement template with a separate field and prescribed amount of space for each criterion.
  - Provide an optional field for reviewers who wish to provide applicants with additional advice ("mentoring") including the opinion that the proposal should not be resubmitted unless fundamentally revised as a new application.
  - Develop appropriate tools, guidance, and training for reviewers for best practices for generating summary statements.

- Shorten and redesign applications to align with the NIH criteria starting with R01, R15, R21, R03, K, and F applications.
  - 12 pages for R01s, with other mechanisms to be scaled appropriately.
  - Structure of application will align with explicit review criteria.

- The use of an appendix of up to 8 pages will be permitted, but only for specific information that is deemed critical on the basis of NIH-defined criteria (e.g., elements for a clinical trial or a large epidemiologic study).

Ensure Balanced and Fair Reviews Across Scientific Fields and Scientific Career Stages and Reduce Burden on Applicants

Dr. Tabak explained that peer review should fairly evaluate proposals from all scientists, regardless of their career stage or discipline, and avoid bias towards more conservative and proven approaches at the expense of innovation and originality. Peer review should: (1) not disadvantage early stage investigators (ESI), (2) apply the appropriate weighting of past performance and future potential for impact as a function of career stage and productivity, (3) be designed to minimize the need for repeated or multiple applications from meritorious scientists to achieve funding support, and (4) encourage "transformative" research. Dr. Tabak noted that the average age of a new R01 investigator is increasing. In 1980, the average age was 37.2 years the average age in 2006 was 42.2 years. A chart illustrating the impact of budget growth on the number of new R01 investigators showed that the number of new investigators proportionately to the NIH budget. Dr. Tabak also presented data from 2002 to 2007 showing that the number of scored applications from first-time investigators is dropping (there were 535 fewer of these applications in 2007 compared with 2002). To address these and related issues, Dr. Tabak presented the following goals:

- Continue to support and develop policies to fund a minimum number of ESI and new (to NIH) investigators, as appropriate.
  - Cluster review, discussion, scoring, and ranking of ESI within a study section.
  - Pilot percentiling ESI across all study sections.
  - The NIH will work to ensure that the number of fully discussed proposals from ESI is not disproportionally reduced.

- For more experienced investigators, place equal emphasis on a retrospective assessment of accomplishments and a prospective assessment of what is being proposed.

- Cluster the review, discussion, scoring, and ranking of clinical research applications within a study section.

- To promote "transformative research," by expanding the Pioneer, EUREKA, and New Innovator awards review experience to encourage risk taking by applicants. Applicants propose ideas with "transformative" potential as a main criterion in concert with a prospective evaluation to measure effectiveness of this approach.
  - Continue to grow the transformative research portfolio to reach approximately 1 percent of R01-like awards.
    - Pioneer and New Innovator award: at least $550 million over the next 5 years.
    - EUREKA award: at least $200 million over the next 5 years.
    - A new, investigator-initiated "transformative" R01 pathway using the NIH Roadmap authority and funding: at least $250 million over the next 5 years.

- Reduce the burden on applicants, reviewers, and NIH staff, by decreasing resubmissions.
  - Reduce the rate of resubmissions from applicants with high likelihood of funding based on A0 review.
  - Reduce the rate of resubmissions for applicants with very low or no likelihood of funding based on A0 review.
  - Establish priorities to carefully rebalance success rates among A0, A1, and A2 submissions to increase system efficiency.
  - Share relevant review and funding data with all applicants (statistics on cumulative success rates as a function of score or percentile will be made part of the summary statement).

In 1998, 60 percent of the awards made were to A2 applications at their first submission and only 10 percent at their second amendment. Those numbers have shifted substantially in the last 10 years. In 2007, 27-28 percent of awards were made to applications at their first submission, compared with approximately 30 percent at their second amendment. Dr. Katz noted that the NIAMS figures parallel these statistics very closely. Dr. Tabak added that almost twice as many rounds of application are required to receive funding today for type 1 R01 applications as compared with 1998. This places a tremendous burden on the peer review system to achieve the same result.

Develop a Permanent Process for Continuous Review of Peer Review

Dr. Tabak said that the NIH peer review process should commit itself to a continuous quality control and improvement process, based on a rigorous and independent prospective evaluation, that encourages adaptive and innovative approaches to review and program management. New models of review, including two-stage reviews (editorial board model) and the use of "prebuttals", will be piloted and evaluated. Different methods for ranking for applications and or reviewers to correct errors in review, the relative merit of applications, and high-bandwidth electronic review also will be piloted and evaluated. In addition, metrics for monitoring the performance of reviews will be developed.

The distribution of R01 PIs by total effort on NIH research project grants and centers, he showed that two-thirds of NIH PIs have 50 percent or less in aggregate percent effort. As opposed to including a "minimum level of effort" for applications, it has been proposed to include a subfield in the "Environment" section of the application where applicants must indicate if they have (or project having) NIH RPG support in excess of $1M (at the time when the current application would be funded). In such cases the applicant must justify why additional resources are being requested at this time. In terms of next steps, an Ad Hoc Peer Review Task Force, chaired by the NIH Deputy Director, will be formed to develop detailed plans and oversee initial implementation. In addition, a new entity is to be formed within the Division of Program Coordination, Planning, and Strategic Initiatives to oversee continuous review of the NIH peer review process.

Discussion

Dr. Katz opened the discussion by acknowledging Dr. Tabak's efforts which will be formally recognized with an award by the NIH Director. Dr. Raisz asked about investigators who would

have good scores but do not receive funding on their initial application. Dr. Tabak describes a proposal that each IC examines the cohort of applicants and analyze whether there is something inherently wrong with these proposals. If so, they should be amended and resubmitted. If the application is "better" but the science will not improve based on resubmission, over the next few years there will be a balancing act that considers these applications against the queue of A1 and A2 applications. ICs will have to look at these issues very carefully. Dr. Katz added that as this new system is transitioned, the adaptive behavior of the study sections will be a major challenge.

Dr. Diamond asked about data on the productivity of funded A2 applications. Dr. Tabak replied that there are many A2 applications that certainly should be funded. However, in his analysis, there was no way to distinguish between the qualities of the research, whether it was carried out at the A0, A1, or A2 level. Dr. Raisz asked whether the data on the aging of R01 investigators included competitive renewals. Dr. Tabak responded that he believed the data included all R01 holders.

Dr. Hahn voiced concern about unqualified reviewers who are not aware of how applications fit with other work in that respective field. She also noted that having 12 review sessions, rather than 18, might be greeted with more enthusiasm on the part of those considering joining a study section. Dr. Tabak explained that efforts are being made to entice the subset of reviewers that the NIH feels are particularly good to continue their service. Dr. Tabak replied that focusing the application and the review on the specific criteria will enable the reviewers to better understand which applications are more likely to have impact on their field. He added that the editorial board review model might circumvent from scoring applications by qualified reviewers.

Dr. Kathleen Green asked about the issue of A2 applications, noting that she has heard that "amended" applications may not exist in certain situations (i.e., the reviewer would not know that an application had been resubmitted). She commented that this might better ensure that the highest quality science gets funded. Dr. Tabak noted that there is a large amount of agreement with this point at the NIH, but there has been a tremendous amount of concern and negative commentary voiced by many extramural scientists and professional organizations against this idea.

Dr. Rosen noted that when these changes to the NIH peer review system are rolled out, it would be important to inform scientific societies and publish these changes. Dr. Katz noted that this information will be published; Dr. Tabak added that this information will appear in an upcoming issue of *Science* with a commentary from Dr. Zerhouni. This information will also be highlighted on the NIH Web site.

X. EXECUTIVE SESSION – BSC REPORT

This presentation was given during closed session.

XI. PORTFOLIO ANALYSIS

A portfolio analysis briefing was given during closed session.