



National Arthritis and  
Musculoskeletal and  
Skin Diseases Advisory Council

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# MINUTES OF MEETING

**September 27, 2007**

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

MINUTES OF THE 63<sup>rd</sup> MEETING

September 27, 2007  
8:30 a.m. to 4:00 p.m.

I. CALL TO ORDER

The 63<sup>rd</sup> meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on September 27, 2007, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 6. Dr. Madeline Turkeltaub, Council Executive Secretary and Deputy Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Extramural Program, called the meeting to order and chaired the first part of it. Dr. Stephen Katz, Director, NIAMS, resumed his duties as Chair upon his arrival later that morning.

**Attendance**

Council members present:

Dr. B. Lee Green  
Dr. Kathleen Green  
Dr. Bevra H. Hahn  
Dr. Joshua Jacobs  
Dr. Brian L. Kotzin  
Dr. Martin J. Kushmerick  
Dr. Robert J. Oglesby (*Ex Officio*)  
Dr. Jack E. Parr  
Dr. Lawrence G. Raisz (by telephone)  
Dr. Clifford J. Rosen (by telephone)  
Dr. Raymond Scalettar  
Dr. Jouni J. Uitto  
Dr. James Weinstein (by telephone)

Council members not present:

Mr. George A. Beach  
Dr. Kevin Campbell  
Dr. Gena Carter  
Ms. Carmen Cheveres DeMummy  
Dr. Betty Diamond  
Ms. Patricia McCabe

## **Staff and Guests:**

The following NIAMS staff and guests attended:

### Staff

Mr. Steve Austin  
Dr. Carl Baker  
Dr. Michael Bloom  
Dr. Amanda Boyce  
Mr. Gahan Breithaupt  
Dr. Eric Brown  
Dr. Branden Brough  
Ms. Justine Buschman  
Ms. Hawa Camara  
Mr. Frank Cromwell  
Ms. Teresa Do  
Ms. Monica Dozier  
Dr. Jonelle Drugan  
Ms. Robin Dupuis  
Mr. Patrick Durand  
Mr. Erik Edgerton  
Ms. Sharon Fair  
Mr. David Fuller  
Ms. Valerie Green  
Ms. Gail Hamilton  
Ms. Meredith Jenkins  
Dr. Dan Kastner  
Dr. Stephen Katz  
Ms. Shahnaz Khan  
Ms. Stephanie Kreider  
Mr. Mark Langer  
Dr. Cheryl Lapham  
Dr. Gayle Lester  
Dr. Helen Lin  
Ms. Anita Linde  
Ms. Mimi Lising  
Ms. Sharon Louis  
Ms. Elizabeth Lordan  
Dr. Kan Ma  
Dr. Marie Mancini  
Dr. Joan McGowan  
Dr. Kathryn Marron  
Ms. Melinda Nelson  
Dr. Steve Notwehr  
Dr. Glen Nuckolls

Dr. John O'Shea  
Dr. Jim Panagis  
Ms. Wilma Peterman Cross  
Dr. Paul Plotz  
Ms. Natalie Reyes  
Ms. Trish Reynolds  
Dr. Louise Rosenbaum  
Dr. William Sharrock  
Ms. Sheila Simmons  
Dr. Susana Serrate-Sztejn  
Ms. Theresa Smith  
Ms. Allisen Stewart  
Ms. Robyn Strachan  
Ms. Yen Thach  
Mr. Michael Toland  
Dr. Madeline Turkeltaub  
Dr. Bernadette Tyree  
Dr. Fei Wang  
Dr. Ping Wang  
Dr. Yan Wang  
Dr. Chuck Washabaugh  
Mr. Elijah Weisberg  
Dr. James Witter

Guests

Mr. Dennis Barbour, Esq., Society for Investigative Dermatology  
Ms. Nancy Botok, McManis and Monsalve Associates  
Ms. Patricia Brandt-Hansberger, Office of Legislative Policy and Analysis, NIH  
Dr. Josephine Briggs, Howard Hughes Medical Institute  
Dr. Lee Baumsithzen, Moffitt Cancer Center  
Mr. Michael Bykowski, Consolidated Solutions and Innovations  
Ms. Diane Christianson, Society for Investigative Dermatology  
Ms. Jodie Curtis, National Psoriasis Foundation  
Ms. Patricia Davidson, Lupus Foundation of America  
Ms. Christy Gilmour, American Academy of Orthopaedic Surgeons  
Ms. Darlene Kerr, Circle Solutions  
Ms. Jennifer McBride, Arthritis Foundation  
Ms. Becky Minillo, Society for Investigative Dermatology  
Ms. Reba Novich, National Osteoporosis Foundation  
Ms. Sheila Rittenberg, National Psoriasis Foundation  
Mr. David Vovakes, Office of the Director, NIH  
Dr. David Wofsy, University of California, San Francisco

## II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept the minutes of the 62<sup>nd</sup> Council meeting, held on June 12, 2007, with no changes.

## III. FUTURE COUNCIL DATES

Future Council meetings are currently planned for the following dates:

January 29, 2008

June 6, 2008

September 23, 2008

February 3, 2009

June 2, 2009

September 16, 2009

Dr. Turkeltaub noted that additional dates through 2010 will be selected in the near future.

## IV. NIAMS IRP DIRECTOR'S REPORT

Dr. John O'Shea, Scientific Director of the NIAMS Intramural Research Program (IRP), and Dr. Dan Kastner, Clinical Director of the NIAMS IRP, provided the annual NIAMS IRP Director's Report to the Council. Dr. O'Shea commented that NIAMS investigators continue to be productive, publishing in prestigious journals and generating exciting data. He highlighted work by Dr. Alasdair Steven and colleagues on retromer structure, explaining that retromers are multiprotein complexes that regulate the transfer of proteins from endosomes to the golgi apparatus. Using a technique called cryo-electron microscopy, the investigators were able to image these multi-protein complexes. This work will be published in the journal *Nature*.

Dr. O'Shea also described advances in T-cell biology made by NIAMS IRP investigators in his laboratory. Naive T cells were thought to have two fates, either as TH1 or TH2 cells. Recent work by Dr. O'Shea and colleagues, however, has shown that T cells are more complex. This work has helped to better explain the pathophysiology of autoimmune disease and gives better insights into host defense. For example, there are other possible lineages of T cells, such as Th17 cells, which make the inflammatory cytokine IL-17 (important in the pathogenesis of diseases such as arthritis, multiple sclerosis, inflammatory bowel disease), and regulatory T cells which suppress immune responses. The researchers have learned a great deal about the regulation of these different subsets, and have begun to relate what has been learned in mice with what happens in humans.

Turning to the accomplishments of NIAMS tenure-track scientists, Dr. O'Shea reported that Dr. Rafael Casellas has a paper in *Nature* that examines the effect of DNA damage on transcription, the signal transduction apparatus involved in this process, and how it might regulate the block in transcription. He and his colleagues used sophisticated imaging techniques such as green

fluorescent protein-labeled polymerase proteins and photobleaching to demonstrate that this process is dependent on the activity of ATM kinase.

Dr. O'Shea commented that although significant progress is being made, challenges remain, such as budget constraints, and with this in mind, the Institute has attempted to maximize cost savings wherever possible. For example, NIAMS has renegotiated its mouse contracts and appointed Melissa Porter of the NIAMS IRP Office of the Scientific Director to run this contract with Taconic. NIAMS is using cost savings to enhance infrastructure. The Institute has established user committees to evaluate its existing cores, improve "customer responsiveness," and ensure that the cores are providing the services that the investigators need. Additionally, a number of capital improvements have been made. For example, NIAMS funds have been used to purchase a Solexa sequencer, and dual photon capability has been added to the Institute's confocal microscope. NIH intramural Roadmap funds were used to acquire an Illumina bead station for use by NIAMS and other investigators who are analyzing DNA or RNA sequences. Dr. O'Shea explained that the Solexa technology is an improved method for sequencing that allows researchers to resequence genomes at 1% of the standard cost. The technology also is effective for understanding epigenetic modifications and examining transcription factor binding on a genome-wide basis. Although the technology cost approximately \$400,000, Dr. O'Shea commented that this purchase was well worth the investment. The high-throughput machine allows investigators to obtain a large amount of information (about 10 billion bases per run) in a very short period of time.

Dr. O'Shea noted that there are a number of ongoing construction projects at NIAMS, with a number of laboratories scheduled to move in early 2008. These moves were paid for primarily through prior year funds and will not have a significant impact on FY 2008 funds.

In terms of personnel, Dr. Michael Ward was recommended for conversion to tenure—he is currently undergoing NIAMS Promotion and Tenure Committee (PTC) review, which will be followed by review from the Central Tenure Committee this fall. Dr. Maria Morasso also was recommended for conversion to tenure and will be reviewed by the PTC soon. Drs. Richard Siegel and David Hall will have their Board of Scientific Counselors (BSC) reviews in early 2008; Dr. Casellas has undergone his BSC review and his mid-tenure review was held in February 2007. With regard to other personnel actions within the NIAMS IRP, Dr. Kastner was appointed as a Tier 4 Senior Investigator—a prestigious appointment as one of the top 10 scientists at the NIH. Dr. O'Shea reported that Dr. Richard Siegel was elected to the American Society for Clinical Investigation. Dr. O'Shea received an award from the Office of Equal Opportunity and Diversity Management. Dr. Mario Cerritelli in the NIAMS Office of Education is trying to establish the NIH Warrior Transition Program with Walter Reed to find positions at the NIH for wounded and disabled soldiers. A number of NIH Institutes and Centers (ICs) have expressed interest in participating. Dr. Cerritelli also is involved in a program with the Montgomery County Police Department to have students involved in NIH programs.

Dr. O'Shea noted that the NIAMS has completed its search for a pediatric rheumatologist—Dr. Raphaela Goldbach-Mansky has been recommended for transition to a tenure-track investigator. The search for an adult rheumatologist will begin soon, and the Institute continues its efforts to recruit an orthopaedic surgeon. In response to a question regarding this recruitment effort, Dr.

O'Shea commented that the Institute is hoping to find a candidate who is interested in being a surgeon but who also has a passion for science and could bring in interesting patients to enrich the activities of the Clinical Center. In response to a question about plans to rebuild the skin IRP at NIAMS, Dr. O'Shea explained that although there are dermatologists on Campus at the NIH, they are primarily at the National Cancer Institute (NCI); there are scientists at the NIH who meet this need, but they are not at NIAMS. He added that this area currently is not a top priority for NIAMS, given current budget constraints.

Dr. Kastner reminded Council members that the Institute is trying to focus its energies in the translational research program of the NIAMS in ways that will take advantage of some of the opportunities available on the NIH Campus (e.g., the Clinical Center). Priorities include conducting studies that provide a greater understanding of the pathophysiology of human diseases, studies of conditions for which it is difficult to assemble adequate cohorts at academic health centers, developing innovative interventional trials in serious disorders for which adequate treatment options do not exist, capitalizing on some of the unique Clinical Center resources (e.g., imaging, laboratory technologies), and developing trans-Institute initiatives for new approaches to some of these issues. Dr. Kastner briefly discussed ongoing work in the following areas:

**Systemic Autoinflammatory Diseases.** Dr. Kastner explained that these disorders are characterized by episodes of fever and inflammation and are distinguished from the traditional autoimmune diseases in that these patients do not have autoantibodies or demonstrable antigen-specific T cells. One of the more severe autoinflammatory diseases, neonatal onset multisystem inflammatory disease (NOMID), is caused by a gene that encodes the pyroptin protein, which is involved in the regulation of IL-1 (NIAMS investigators linked this gene to NOMID). Patients with this condition have a hives-like skin rash, fever, and many develop a bony overgrowth starting at 6 months to 1 year of age. More seriously, these patients also have inflammation of the central nervous system, which can lead to increased intracranial pressure, chronic meningitis, blindness, deafness, and learning disabilities. Dr. Mansky and colleagues published a paper in the *New England Journal of Medicine* on a study of 18 patients (representing a large percentage of the NOMID patients of a suitable age to be treated in the United States) over 6 months examining treatment with the IL-1 receptor antagonist anakinra. The results were dramatic; the skin rash disappeared in these patients within 1-2 days, as did the fever. There also was evidence that the chronic meningitis disappeared after 2-3 months of treatment. This treatment has had a life-changing impact on these patients, who have been followed since the study was started (3 years post-treatment for some patients). Their growth curves are starting to correct, although there has been no major impact on the bony overgrowth—Dr. Kastner speculated that earlier intervention might make a difference in this regard.

In addition, NIAMS sees a large number of patients who have undiagnosed inflammatory conditions or recurrent fevers. On referral, more than 950 patients with unexplained febrile syndrome have been seen by NIAMS IRP clinicians. Samples have been analyzed from an additional 850 patients. Only about one-third of the patients seen by NIAMS clinicians or for whom samples were submitted have a mutation in one of the genes that is known to cause these conditions (i.e., fully two-thirds of the patients do not yet have a genetic explanation for this condition). Much work remains in terms of understanding the pathophysiology of the disorder. NIAMS IRP investigators are developing a resequencing chip that will allow them to scan 90

different genes—only four of which are genes known for recurrent fever syndrome—in the hopes that mutations in the other genes can be linked with additional phenotypes. Shar-Pei dogs have a recurrent fever syndrome similar to some of the diseases seen in humans. NIAMS has established a collaboration with the Broad Institute at the Massachusetts Institute of Technology and Harvard University to conduct a genome-wide scan looking for Shar-Pei fever genes in the hopes that findings may be related to humans. Promising data from candidate genes are emerging.

NIAMS IRP investigators also working to answer the question of why diseases such as familial Mediterranean fever (FMF) are common in certain populations. Dr. Kastner speculated that mutations may confer a selective advantage against some type of infectious organism. These mutations are thought to alter residues that form a “pocket” on the pyrin protein; NIAMS researchers are interested in whether this pocket binds to malaria parasites and are conducting collaborative *in vitro* studies with researchers at the National Institute of Allergy and Infectious Diseases to determine whether patients with FMF have an increased resistance to malaria.

**Genetics of Complex Rheumatic Diseases.** Dr. Kastner explained that many common diseases in rheumatology are complex and caused by interactions of more than one gene, which oftentimes are affected by the environment. Until fairly recently, this was, for the most part, an intractable problem. However, with advances in the genome project and high-throughput single nucleotide polymorphism analysis, this is no longer the case. Dr. Elaine Remmers of NIAMS’ IRP is working as part of the North American Rheumatoid Arthritis Consortium (NARAC) and discovered that STAT4 (a gene involved in coding a protein that signals and T cells and seems to be involved in the development of TH1 and TH17 cells) is associated with an increased risk of developing systemic arthritis and lupus. Individuals with one copy of the variant gene have an approximate 35% increased risk of developing rheumatoid arthritis; two copies result in a 60% increased risk. Also, one copy of the variant gene yields a 60% increased risk of developing lupus, while 2 copies results in a 2.5 times greater risk of developing lupus than that of the general population.

NIAMS IRP investigator Dr. Michael Ward has a study to be published soon in *Nature Genetics* on susceptibility to ankylosing spondylitis, a common rheumatic disease caused by the interaction of more than one gene. The gene ARTS1 is associated with risk of developing the disorder. The gene is involved in the processing of antigen associated with a major histocompatibility complex and in the cleavage of tumor necrosis factor off the cell surface. NIAMS IRP researchers are interested in examining the genes for other rheumatic diseases, Behcet’s Disease, for example. Behcet’s Disease is caused by multiple unknown genes and is an autoinflammatory disease characterized by ulcers in the mouth, ocular inflammation, and genital ulcers as well as other skin manifestations, arthritis, and central nervous system disease. The disorder is seen in a geographic distribution through Turkey and the Mediterranean Basin into the Far East. Dr. Kastner explained that using the newly acquired Illumina bead station, NIAMS investigators hope to map genes that confer susceptibility for Behcet’s Disease.

**Clinical Trials on Outcome Studies.** The NIAMS IRP is involved in a number of clinical trials on outcome studies. Dr. Kastner highlighted two of them, treatments for inflammatory myositis,

and outcomes research on the probability of developing diabetes in rheumatoid arthritis patients taking hydroxychloroquine.

**Rejuvenation and Expansion of Pediatric Rheumatology.** Dr. Kastner noted that the NIAMS IRP has a strong interest in enhancing pediatric rheumatology capabilities at the Institute. As noted earlier, Dr. Goldbach-Mansky has been appointed to a tenure-track position, and there also are ongoing discussions with an extramural senior pediatric rheumatologist. The Institute also has recruited a pediatric hospitalist and a pediatric nurse practitioner.

**Senior Staff Recruitments.** In terms of new NIAMS senior recruits, Dr. Mark Gourley has been named the new Director of the Rheumatology Training Program. The Institute is moving forward with recruitment of adult rheumatology physician scientists and clinical trialists once the previously mentioned pediatric recruitment is complete.

**Inter-Institute Initiative in Immunology and Inflammation.** Dr. Kastner explained that one area of great concern to the NIAMS IRP is the use of the NIH Clinical Center. The Center's capacity is approximately 234 beds but it is not being used to its fullest potential. On the inpatient side, only 64% of the beds are being used. Outpatient and day hospital capacity uses are even less. To help enhance use of the Clinical Center and reinvigorate clinical activities, NIAMS and other ICs are developing an inter-Institute program in immunity, inflammation, and infectious diseases. The many different subspecialties within the NIH intramurally that deal with immunologic disease do not always communicate. The concept behind this new initiative is to bring these experts together in a program with targeted collaboration to study common pathophysiologies and develop new immune-based therapies that might transcend specific subspecialties and apply to many of them. The initiative is envisioned to be similar to the Broad Institute model, where researchers would be brought together to interact on a close basis, with the hope that there would be ample opportunity for extramural experts to participate through sabbatical activities or as visiting scholars. It also is hoped to include the pharmaceutical industry in these efforts.

**Developing Clinical Research “Manhattan” Projects.** Dr. Kastner explained that as a way to grow the intramural clinical programs, each IC is trying to identify clinical research “Manhattan” projects—audacious, big problems that have not been adequately addressed at any other venue to date and that could use the resources of the Clinical Center. NIAMS IRP staff are currently considering such projects, and Council members were asked to submit any suggestions for potential projects.

## **Discussion**

Council member Dr. Clifford Rosen, Executive Director of the Maine Center for Osteoporosis Research and Education, asked about projects that include visiting investigators and how that might operate. Dr. Kastner explained that for established senior university-based investigators, it may be difficult to move to Bethesda for a year, so other types of models have been considered, such as “1-week-per-month,” or “a few weeks every few months” to collaborate with established intramural investigators in the hopes of creating an ongoing interaction. Dr. Lawrence Raisz, Director of the University of Connecticut Center for Osteoporosis and a member of the Council,

commented that for such an initiative to be successful, it should have origination from both sides, so that there would be an opportunity to work together, and in a sense, there would be a Request for Applications issued for coming to the NIH. Dr. Kastner added that if there was a great deal of interest in this activity, some type of vetting process would be needed that would include a committee to review applications.

At this point in the discussion, Dr. Katz arrived at the meeting and took over as Chair.

Council member Dr. Jouni Uitto, Professor and Chair of the Department of Dermatology and Cutaneous Biology at Jefferson Medical College, asked about the underutilization of the Clinical Center. Dr. Kastner noted that the number of tenured individuals conducting clinical research has decreased in recent years, adding that for many researchers seeking tenure, a laboratory-based trajectory is more attractive than a patient-oriented trajectory. Dr. Uitto also asked about the costs associated with using the Clinical Center. Dr. Kastner explained that in the early 1990s, it was a fee-for-service arrangement. Starting in about 1996, a “school tax” approach was taken, so that each IC is charged the same amount proportional to their intramural budget. It is hoped that this approach does not discourage recruitment of patients to protocols involving the Center. Dr. Katz added that this “school tax” model currently is being evaluated at the NIH level. He also commented that an additional limiting factor to use of the Clinical Center is the dearth of drug company studies—it is much more difficult to conduct these types of studies at the Clinical Center. Dr. O’Shea added that there is no income generated by patients coming into the Clinical Center. Dr. Katz explained that he and NCI Director Dr. John Niederhuber lead a group that is addressing issues related to better utilization and more rational and modern utilization of the Clinical Center. The initial primary focus is to find people, space, and resources.

Dr. Brian Kotzin, a member of the Council and Vice President of Medical Sciences at Amgen, Inc., asked if there was going to be any effort at NIAMS to determine responsiveness to therapies now that different polymorphisms have been identified that lead to susceptibility to rheumatoid arthritis and other diseases. Dr. Kastner commented that the Institute is very interested in this work, and that NARAC is developing studies along those lines as well.

Council member Dr. Bevra Hahn, Professor in the Department of Medicine at the University of California, Los Angeles School of Medicine, asked whether there were any strategies in place to access pharmaceutical industry data that exist on responsiveness to therapies for common diseases. Dr. Katz noted that this has been discussed often with the U.S. Food and Drug Administration (FDA), and that there is a clear barrier here. However, at least in terms of inflammatory pulmonary diseases, this has been done to a certain level and some members of the pharmaceutical industry have had discussions about conducting activities at the pre-competitive level.

## V. DIRECTOR’S REPORT AND DISCUSSION

Dr. Katz welcomed Council members, NIAMS staff, and guests. He began his report by inviting them 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 this month focuses on the

demonstration project “Check Up On Your Bones,” an interactive bone health tool that is accessible on the NIAMS Web Site. Dr. Katz expressed his enthusiasm about the large number of voluntary organization representatives in attendance.

Before beginning his formal remarks, Dr. Katz also acknowledged and thanked the following outgoing Council members, presenting each with a plaque: Dr. Uitto; Dr. Jack Parr, Consultant for Medical Technology Development, Inc.; Dr. Raymond Scalettar, Clinical Professor of Medicine at George Washington University; and Dr. Kotzin. Dr. Katz noted that each member has made essential contributions to the Council’s deliberations.

### **Personnel Changes at the NIH and NIAMS**

At the NIH level, Dr. Alan Krensky has joined the NIH as Director of the Office of Portfolio Analysis and Strategic Initiatives (OPASI) within the NIH Office of the Director. Dr. Krensky previously served as Professor of Pediatrics, Chief of the Division of Immunology and Transplantation Biology, Associate Chair for Research in the Department of Pediatrics, and Associate Dean for Children’s Health at Stanford University.

Within the NIAMS Office of the Director, the Institute is continuing its national search for a Deputy Director; in the interim, Dr. Paul Plotz of NIAMS’ IRP continues to serve as the Institute’s Acting Deputy Director. Ms. Robin DiLiello has joined the Institute as a Senior Budget Analyst (Ms. DiLiello previously worked in the Budget Office within the NIH Director’s Office). The Institute also has welcomed two new Science and Technology Policy Fellows of the American Association for the Advancement of Science—Dr. Branden Brough who recently completed a post-doctoral fellowship in the Laboratory of Muscle Biology within NIAMS’ IRP, and Dr. Steve Nothwehr, who comes to the NIAMS from the University of Missouri, where he is an Associate Professor in the Division of Biological Sciences. Mr. David Fuller, who is in the NIH Administrative Fellows Program, also has joined the Institute. In addition, Ms. Hawa Camara and Ms. Meredith Jenkins have joined NIAMS as Special Volunteers in the Office of Communications and Public Liaison. Both are Community Health Education majors in the Department of Public and Community Health at the University of Maryland, College Park.

In the NIAMS Extramural Research Program (ERP), Dr. Kathryn Marron recently joined the NIAMS as a Research Program Analyst in the Skin and Rheumatic Diseases Branch. The Institute also welcomes Ms. Regina Mong as a Senior Administrative Officer within the NIAMS ERP.

Dr. Katz acknowledged staff from the NIAMS Grants Management Office who were in attendance. He commended them for their efforts, particularly towards the end of the fiscal year. These staff members included Melinda Nelson (Chief of the Grants Management Office), Steve Austin, Teresa Do, Erik Edgerton, Gail Hamilton, Mark Langer, Sheila Simmons, Yen Thach, and Natalie Reyes.

## Update on Budget and Congressional Activities

Dr. Katz reported that both the House and Senate Appropriations Committees have completed markup of the FY 2008 appropriations bills for the Departments of Labor, Health and Human Services, Education and Related Agencies. The House bill includes \$29.6 billion for the NIH, which is \$1 billion more than the President's request and \$750 million over the FY 2007 comparable amount. The Senate mark provides \$29.9 billion for NIH, an increase of nearly \$1.3 billion above the President's request and \$1 billion above the comparable FY 2007 level. The allocation for NIAMS proposed by the House is \$516 million, which is an increase of \$7.8 million and 1.5 percent over FY 2007. The amount proposed by the Senate for NIAMS is \$519.8 million, which represents an increase of \$11.6 million and 2.3 percent over FY 2007.

Dr. Katz also explained that the NIH will operate under a Continuing Resolution through November 16, 2007. In recognition of the growing importance of the NIH Common Fund, and in an effort to provide greater transparency, two changes were instituted in the FY 2007 joint funding resolution. The first change specified that the exact amount appropriated for the Common Fund would be in bill language. The second change shifted the practice of transferring a certain percentage of each IC's appropriation to the fund.

Dr. Katz noted that there were a total of 262 competing Research Project Grant (RPG) awards in FY 2007, at a success rate of approximately 19%, which is similar to last year's rate. The number of new R01 awards represents about 60% of the new RPGs. There were a total of 38 awards made to new investigators, representing 35% of all new R01 awards and about 23% of all NIAMS R01 awards. Dr. Katz explained that over the last 5 years, the NIAMS has averaged 41 new investigator awards. In FY 2007, 39 new investigators are being supported through 38 awards. This number is higher than the average number of new investigators supported at other ICs.

On July 16, as part of a series of Capitol Hill briefings sponsored by the Association of American Medical Colleges, Dr. Katz gave a talk on osteoarthritis research to a group of Congressional staff. He was joined by Dr. Farsh Guilak of Duke University, who described novel work his laboratory is conducting to develop 3-dimensional scaffolds that could potentially be used to patch damaged joint surfaces for the benefit of patients with osteoarthritis. On September 12, the NIH and National Aeronautics and Space Administration (NASA) held a signing ceremony to formalize an agreement to facilitate biomedical research on the International Space Station. NIAMS coordinated the development of this agreement (Dr. Katz serves as the NIH liaison to NASA, and as a member of the NASA Administrator's Advisory Council). NIH Director Dr. Elias Zerhouni was joined by NASA Administrator Dr. Mike Griffin, in addition to Senators Kay Bailey Hutchison (R-TX), Barbara Mikulski (D-MD), and Bill Nelson (D-FL).

As a follow-up to Congressional report language, the NIAMS recently released *The Future Directions of Lupus Research*, a planning document developed with a large amount of input from scientific experts from the lupus research community. The document highlights promising opportunities to increase the understanding of lupus at the population, individual, and molecular levels. It focuses on five major areas of research: (1) disease etiology; (2) innate immunity, acquired immunity, and inflammation; (3) target organ damage; (4) pediatric lupus, special

populations, and health services research; and (5) diagnosis and treatment. A number of NIAMS staff provided their expertise and leadership in developing the document.

### Highlights of Selected Recent Scientific Advances

- Dr. Elaine Fuchs and colleagues published a paper on molecular signals that maintain skin stem cell properties (*PNAS*). The researchers found that bone morphogenic protein (BMP) maintains the quiescence of hair follicle stem cells. Other molecular signals then activate hair follicle stem cells to proliferate. BMP is turned off during this period of proliferation, but it is turned on again to stop the cell division and stimulate differentiation of the cells, to form functional hair follicles.
- Dr. Regis O’Keefe and others studied a structural bone allograft combined with genetically engineered mesenchymal stem cells as a novel platform for engineering replacement bone. (*Tissue Engineering*).
- Dr. Richard Gallo and colleagues found that increased serine protease activity and cathelicidin promotes skin inflammation in rosacea (*Nature Medicine*). The researchers noted that increased levels of cathelicidins in rosacea skin lesions, as well as increased levels of stratum corneum tryptic enzyme, appear to contribute to the chronic inflammatory response that characterizes this condition.
- Studies from Dr. Chandra Mohan and colleagues have examined coordinated immune cell communication in mouse models of lupus, focusing on the mammalian target of rapamycin, or mTOR, which was found to reduce the disease severity and decrease the activity of several of the signaling pathways (*Journal of Clinical Investigation*). Notably, this mTOR inhibitor and other similar drugs are already being tested in clinical trials for a variety of diseases, such as different types of cancer and organ transplant rejection.
- A retrospective chart review of military medical records revealed that symptoms and organ-associated autoantibodies precede the diagnosis of lupus (*Arthritis & Rheumatism*). Drs. John Harley and Judith James found that autoantibodies, which are commonly found in lupus patient serum, were harbingers of lupus-associated kidney disease in a subset of patients. Arthritis was the most common clinical symptom observed prior to the onset of lupus. Some biological response modifier therapies for arthritis could be cause for concern in managing lupus patients. More accurate preclinical diagnosis of lupus could avoid inappropriate and potentially harmful treatments, and possibly pre-empt emergence of disease.
- In the area of muscle physiology, Dr. Grace Pavlath and colleagues have identified prostacyclin as an important factor in muscle cell repair (*FASEB*). Prostacyclin was shown to reduce myoblast motility, which was determined to increase the rate of muscle repair. Prostacyclin is produced by Cox-1 and -2 which are inhibited by common anti-inflammatory drugs. Therefore, the use of such drugs could result in a reduced rate of muscle repair.

- Dr. Kevin Campbell and colleagues reported in *Molecular Therapeutics* on the long-term skeletal muscle protection after gene therapy in a mouse model of limb-girdle muscular dystrophy. Currently, there are no treatments for this disease; however, in the type 2D version, a new recombinant viral vector has been developed that increases efficacy to over 1 year in mice (previous approaches were limited to a few weeks).
- A group of investigators has found that the hypoxia-inducible factor alpha pathway couples angiogenesis to osteogenesis during skeletal development (*Journal of Clinical Investigation*). Mice with increased levels of hypoxia-inducible factor (HIF) in osteoblasts were found to develop denser bones featuring a greater number of blood vessels. Because HIF is known to induce production of vascular endothelial growth factor (VEGF) and bone growth requires adequate blood supply, the following mechanism is proposed: low oxygen levels stimulate HIF production in osteoblasts which promote VEGF, causing blood vessel growth that enables bone growth.

### **NIH/NIAMS Activities and Plans for the Future**

With regard to the NIH Roadmap 1.5, trans-NIH working groups are developing proposed initiatives for FY 2008 in the areas of microbiome and epigenetics. There also are ongoing discussions about the best way for the NIH to facilitate activities in protein capture agents and proteomics as well as in the standardization of human disease phenotypes. In addition, a number of areas for further collaboration and coordination across NIH are being pursued. Dr. Katz reminded Council members that one of the groups that will be advising the NIH about cross-cutting areas of science is the “Council of Councils,” a new committee that OPASI is convening on behalf of Dr. Zerhouni. Council member Dr. Bevra Hahn will represent the NIAMS Council on this group, and will serve as a liaison between the two Councils. The first meeting of the Council of Councils is scheduled for November 8, 2007; Dr. Hahn was asked to provide an update to the Council at the January 2008 meeting.

Dr. Katz reported that NIAMS is leading a mid-course review of the Patient-Reported Outcomes Measurement Information System (PROMIS) Initiative, a Roadmap project designed to re-engineer the clinical research enterprise. Dr. Lee Simon, a noted rheumatologist from Boston who is an expert in health outcomes research, served as Chair of the expert panel that conducted the review. The panel recently submitted its final report, and will be presenting its recommendations to the trans-NIH Roadmap governance group in mid-October. At the next Council meeting, Drs. Susana Serrate-Sztejn and Jim Witter of NIAMS’ Division of Skin and Rheumatic Diseases will provide an update on the PROMIS Initiative and its future direction. Dr. Katz also noted that Ms. Anita Linde and Dr. Louise Rosenbaum of the NIAMS Office of Science Policy and Planning were instrumental in coordinating the mid-course review.

The NIH recently announced the second set of Clinical and Translational Science Awards (CTSAs). Twelve new awards have been added to the original 12 that were announced last October. Of the 12 new awards, two are of particular interest to the Institute. Dr. Mark Dresner of the University of Wisconsin and Dr. Dan Clauw at the University of Michigan are both Principal Investigators on CTSAs. Overall, four of the 24 PIs from the CTSAs are grantees of the NIAMS. Dr. Zerhouni also recently announced new recipients for the NIH Pioneer Awards

and New Innovator Programs. A total of 41 exceptionally innovative investigators, many of whom are in the early stages of their careers, were selected for 5-year grants totaling more than \$105 million.

Earlier this month, the NIH announced its plans to implement the President's recent Executive Order related to stem cell research. Dr. Story Landis, Director of the National Institute of Neurological Disorders and Stroke, chairs the NIH Stem Cell Task Force. At the NIAMS level, Dr. Carl Baker of the NIAMS Division of Skin and Rheumatic Diseases represents the Institute on the Stem Cell Implementation Working Group.

A number of the diseases that the NIAMS supports research on are now represented in the Genome-Wide Association Studies (GWAS). National Heart, Lung, and Blood Institute Director Dr. Betsy Nabel led the NIH-wide effort to develop a GWAS data sharing policy. NIAMS was represented on this working group by Dr. Bill Sharrock, who has a long-standing interest and considerable expertise in this area.

Dr. Katz reported that in terms of the Osteoarthritis Initiative (OAI), baseline and 12-month follow-up images for the first 2,686 participants, and baseline clinical data for the entire cohort of nearly 4,800 participants, are now available. More than 600 researchers from 41 different countries have registered to use the OAI data. Dr. Gayle Lester of NIAMS' Division of Musculoskeletal Diseases has led the OAI effort with considerable input from Dr. Joan McGowan, also of NIAMS' Division of Musculoskeletal Diseases.

### **Highlights of Information Dissemination Efforts**

Council members were provided with a CD-ROM for health professionals and the general public, titled "Bone Health Information for You and Your Patients." This CD-ROM provides easy access to the latest information on bone health and diseases. Council members also received a 2008 Pocket Calendar, "Tips and Resources for Healthy Bones for Life." This calendar was produced by the NIH Osteoporosis and Related Bone Diseases ~ National Resource Center and features health resources from the Institutes funding that Center.

### **Discussion**

Council member Dr. Lee Green, Executive Director of the Office of Institutional Diversity and Research and Professor of Health Outcomes and Behavior at the H. Lee Moffitt Cancer and Research Institute, asked about a bill introduced by Senator Kennedy and whether its intent was to foster more relationships between the NIH ICs and National Center for Minority Health and Health Disparities. Ms. Wilma Peterman Cross, Deputy Director of the NIAMS Office of Science Policy and Planning, indicated that this is the intent of the bill, and that she would provide Council members with additional information. Council member Dr. Josh Jacobs, an orthopaedic surgeon at Rush University Medical Center, asked if there was any followup information available on the Arthritis Prevention Control and Cure Act of 2007, which was briefly discussed at the last Council meeting. Ms. Peterman Cross indicated that there has been little Congressional activity on disease-specific bills, and that most activity has been focused on gathering cosponsors.

## VI. TRAINING EVALUATION WORKING GROUP REPORT

Dr. David Wofsy, Chairman of the NIAMS Training Grant and Career Development Award Program Evaluation Working Group, noted that his group was asked to address the following two overarching questions:

- How successful has each component of the training program (T32, F32, K01, K08) been in maintaining the pipeline of researchers in the NIAMS mission areas?
- Is the existing structure still appropriate to meet current and projected training needs?

The Working Group defined success within the context of this review from the perspectives of trainees, programs, and NIAMS. In terms of trainees, success was defined with research as a primary focus of an individual's career (in academia, industry, or government) or as a secondary career focus (e.g., educators in a research environment, clinicians who contribute to research). With regard to programs, success was defined in both quantitative measures (e.g., the percent of recipients who achieve success as defined for trainees) as well as in qualitative measures (e.g., the importance of the research, breadth of research activities, responsiveness to the scientific environment, etc.). For NIAMS, success also was defined in terms of quantitative measures (e.g., percent of trainees and programs that achieve success) and qualitative measures (e.g., impact on public health, breadth of programs, recruitment of promising investigators, effective strategic planning for the future).

Dr. Wofsy noted that the Working Group was impressed by the success of each component of the training program (T32, F32, K01, K08), all of which exceeded expectations in each case. He emphasized that many important questions could not be answered with the available data and methodology. To help address this issue, the Working Group proposed that NIAMS design and implement prospective mechanisms to assess the success of individual trainees, institutional training programs, and each component of its own training portfolio. Dr. Wofsy suggested that this activity could be carried out as a research project.

In terms of methodology, an outside contractor conducted the data collection from public and NIH databases. From the electronically available information, efforts were made to glean outcome information in terms of the career outcomes of trainees. Interviews were conducted with NIAMS ERP staff as well. The study focused on a sample of trainees in the following areas: (1) post-doctoral T32 grants in 1993-1994 (n=109), (2) post-doctoral F32 grants in 1993-1994 (n=44), (3) K01 awards in 1995-1996 (n=6), and (4) K08 awards in 1995-1996 (n=58).

With regard to the Working Group's definition of success for individual trainees, 75% of the T32 awardees, 84% of the F32 recipients, 100% of the K01 recipients, and 100% of the K08 awardees were in science-related careers. Additionally, 55% of the T32s, 75% of the F32s, 100% of the K01s, and 62% of the K08s were currently active in research as suggested by their current job title. There was evidence of recent (within 2 years) publication activity for 50% of T32s, 59% of F32s, 83% of K01s, and 85% of K08s. Dr. Wofsy emphasized that these are rough approximations given the nature of the available data, and that small discrepancies within these numbers should not be a focus. In terms of R01s, 17% of T32s, 34% of F32s, 83% of K01s, and

55% of K08s in the sample received R01 grants. Dr. Wofsy noted that the success rates reflected a logical continuum, with a lower percentage of T32 trainees establishing independent research careers than F32, K01, and K08 awardees.

Dr. Wofsy emphasized that there were important questions that could not be answered given the data. For example, there are no comparisons of the distinct areas of NIAMS' mission, and no way to assess a cause-and-effect relationship between training components and eventual success. No analysis of NIAMS' performance relative to other NIH ICs was carried out. In addition, there are inadequate data regarding qualitative measures and no data regarding long-term retention. The applicability of a retrospective analysis to determine future needs in a changing landscape is questionable.

Dr. Wofsy then presented the following recommendations formulated by the Working Group:

- Establish a structured data collection mechanism to support ongoing evaluation of training program effectiveness. This could be accomplished as a research project with prospectively defined questions and a methodology to answer them.
- Acknowledge the economic aspects of research by providing more flexibility on the percent effort required for K awards to accommodate clinical responsibilities and other personal and professional circumstances, and by lifting the restrictions that limit other sources of funding.
- Avoid imposing a time limit from completion of degree on applications. Maintain flexibility and discretion of the peer review board to reward outstanding candidates.
- Build on current success of the Training Grant and Career Development Award Program—as well as the recent increase of participants in NIAMS mission-related programs—by increasing the funding for NIAMS training grant mechanisms. The pipeline of researchers cannot be expanded unless the number of awards and the amount of funding is also increased. Dr. Wofsy noted that the Working Group acknowledged that it understands that putting more resources into one area often entails taking resources from another. The Working Group did not look at the overall portfolio or make value judgments, and Dr. Wofsy stressed that this is not a recommendation to divert funds from R01s to the training program.
- Consider integrating a new component into NIAMS institutional training grant strategy that would address the related dilemmas of prolonged training followed by multiple application cycles in pursuit of a K award, which were seen as major deterrents to a career in science.
- Increase the NIAMS budget for R01 grants so that there are more opportunities for trainees to conduct independent research at the end of the pipeline.
- Centralize training information to make information on different mechanisms more accessible to potential applicants. Encourage collaborative interaction with professional and constituent organizations to develop a robust complementary portfolio of training funding.

- Structure the criteria for success in grant review to encourage and reward integrated and interdepartmental approaches, foster innovation, and support interdisciplinary mentorship in applications. Reinforce the value of grant writing and management in program curriculum.
- Reinforce the value of mentorship by providing a range of opportunities (e.g., annual meeting at NIAMS, Web-based modules, etc.) that support training of mentors as well as trainees, and that foster an environment of collaboration and support for mentors and those being mentored.
- Work with other NIH Institutes and private foundations to ensure that there is a comprehensive and complementary portfolio of funding mechanisms for trainees.

## Discussion

Dr. Katz noted that at a recent American Society for Bone and Mineral Research meeting, a very effective presentation on submitting grants geared toward the young investigator was given and could be very helpful for educating newer investigators. He asked if the fifth recommendation presented by Dr. Wofsy was suggesting that there should be decisions made at earlier points to increase success rate of K awards. Dr. Wofsy explained that the idea behind this recommendation is to identify the best people early and invest in them, so that they know where they stand. Some of the Working Group members thought there should be an institutional ability to give a K award in the same way the institution decides who gets a T32 award (i.e., an institution could identify someone at the beginning of the process and commit to them 5 years of support). Other Working Group members were in favor of a bridge in the T32, so that at the end of getting 2 years of T32 support, investigators are supported at the K level for 2 years while they submit their K application(s). Still other Working Group members advocated putting money into mechanisms that already exist and are successful (e.g., K08, K01) rather than creating additional mechanisms. Overall, Dr. Wofsy reported, the Working Group identified a problem with the dilemmas of prolonged training followed by multiple application cycles in pursuit of a K award, but could not come up with an agreement on a solution.

Dr. Katz explained that the K12 award is given to an institution to provide K awardees at the local level. He has had discussions with academic health centers that have asked to select the awardees themselves. However, Dr. Katz indicated that giving this level of decision making to Deans typically is not a good return on investment, because the Institute's priorities aren't necessarily the Deans' priorities. Dr. Wofsy agreed, adding that those on the Working Group who suggested having the institutions select the awardees indicated that the K12 award did not address this need. He emphasized that the Working Group is not suggesting that K12 awards be made and the responsibility of selecting the awardees be given to Deans' offices. He explained that some of this concept, however, could be integrated into the training grants that the Institute receives for NIAMS-related investigators.

Dr. Jacobs stressed the importance of the first recommendation (to establish a structure for the data collection process), noting that there are many gaps in the data presented and as such, it is difficult to reach conclusions based on them. For example, it is not possible to determine how different sectors of the Institute compare to each other. He asked if there are any data on how

M.D. investigators fare versus Ph.D. investigators, and how the Working Group defined the term “clinician.” Dr. Wofsy explained that the Working Group decided that if an individual was functioning as a clinician in an academic environment, and their name is on a clinical paper, they are categorized as a clinician. In terms of M.D. and Ph.D. investigators, Dr. Wofsy noted that it is difficult to draw conclusions based on the small amount of data, but there are indications that there is a better retention rate of Ph.D.s (although the difference was not statistically significant).

Dr. Hahn asked if a more rapid turnaround of applications for K awards, with the goal of letting applicants rewrite within 3 or 4 months after a rejection, would address the same issues a bridging grant would address. Dr. Wofsy indicated that this is an psychological step, to be able to say to a person, “we have faith in you, we are going to invest in you, if you stick with us, here is how we are going to support you,” and to let them know that early. It does not address all of the problems though. Dr. Wofsy explained that it is appropriate to fail people when the situation warrants it, but failure should not be the system’s focal point. Somehow the message must be conveyed that “no” is not necessarily the end. He explained that most people who succeed are first told “no.” He added that in his opinion, many investigators are lost at this level—there is an accumulative effect that finally takes someone out of research. Often it is not the day they get their first refusal, it is the point at which they decide that they cannot go on another year wondering what is going to happen.

Dr. Serrate-Sztein noted that a few Council meetings ago, there was a presentation from the Center for Scientific Review (CSR) on applications by new investigators and established investigators in clinical research. One of the points made was that there appears to be greater experience in the basic research applicant pool and that there seems to be greater resilience from non-clinical researchers in terms of revising and resubmitting applications. Dr. Katz added that there is a tremendous disparity between those who are conducting clinical research and submitting renewal for first R01s compared with those doing more basic research.

Council member Dr. Kathleen Green, Joseph L. Mayberry Professor in the Department of Pathology/Cancer Center at Northwestern University Medical School, pointed out that evaluating training is a very important effort and echoed the sentiment that it is important to expand the data set beyond the window examined by the Working Group in the future. She suggested that there are fewer Ph.D.-level researchers in training programs now compared with years past. Dr. Wofsy indicated that some of the data support this. Dr. Raisz asked if K23 awards were included in the analysis. Dr. Katz responded that these awards have only been in existence for about 7 years, and that they were excluded from the study.

Dr. Parr asked whether there were any data available on where the 217 people included in the study are in their careers, and whether the Working Group examined the patient literature. Dr. Wofsy indicated that data on the career choices of those included in the study are included, but that the group did not review the patient literature.

Dr. Jacobs asked if the Working Group considered the K99 award and whether it would be a possible solution to the fifth recommendation. Dr. Wofsy noted that the K99 award was not included in the analysis. Dr. Katz explained that the K99 awards are very selective; it is not clear how this mechanism will affect this type of analysis in the future. Dr. Turkeltaub added that

with the K99 awards, there will be the ability to carry out prospective data collection. Dr. Lee Green asked if the Working Group collected any data on women and minority investigators. Dr. Wofsy noted that the Working Group felt strongly that these are important data to have. The group's report includes information on gender, race, and national origin.

## VII. PEER REVIEW EVALUATION

Dr. Larry Tabak, Director of the National Institute of Dental and Craniofacial Research, presented the results of a self-study by the NIH in partnership with the scientific community to strengthen peer review in changing times. He noted that the increasing breadth, complexity, and interdisciplinary nature of biomedical science are creating new challenges for the system used by the NIH to support biomedical and behavioral research. Peer review is a key component of the system. The mandate of the group tasked with evaluating peer review at the NIH was to look not just at peer review, but also at the total support system. Dr. Tabak emphasized that the NIH must: (1) continue to adapt to rapidly changing fields of science and ever-growing public health challenges, (2) work to ensure that the processes used to support science are as efficient and effective as possible for applicants and reviewers alike, and (3) continue to draw the most talented reviewers.

Dr. Tabak explained that broad input is being sought from a wide variety of stakeholders, including investigators, scientific societies, grantee institutions, and voluntary health organizations. The NIH also has been obtaining input from its own staff—many NIAMS staff have provided valuable comments and participated actively in this process. Two groups are leading these efforts: (1) a working group of the Advisory Committee to the Director (ACD), co-chaired by Dr. Tabak and Dr. Keith Yamamoto of the University of California, San Francisco, that includes membership external to the NIH; and (2) an internal NIH Steering Committee Working Group (SCWG) on Peer Review, co-chaired by Dr. Tabak and Dr. Jeremy Berg, Director of the National Institute of General Medical Sciences. The CSR is involved in a number of current initiatives dealing mostly with mechanical elements of the peer review process. These initiatives include: (1) shortening the review cycle, (2) immediate assignment of applications to integrated review groups, (3) realignment of study sections, (4) electronic reviews, and (5) shortening the size of applications. The SCWG is coordinating its efforts with CSR's initiatives.

During the diagnostic phase of these activities, when broad input was sought, the NIH issued a Request for Information (RFI) and created an interactive Web site for soliciting opinion from the period of July-September 2007. The RFI included questions on the challenges of the NIH system of research support, challenges of the NIH peer review process, solutions to challenges, core values of the NIH peer review process, peer review criteria and scoring, and career pathways. Dr. Tabak noted that feedback can still be provided through the following e-mail address: PeerReviewRFI@mail.nih.gov. To date, more than 2,500 responses from the various stakeholder communities have been submitted.

In addition to the RFI, two "Deans teleconferences" have been held with approximately 100 participants. There also have been a series of regional town meetings held across the Nation; one meeting involved professional organizations, one engaged patient advocacy groups, and three

meetings focused on input from investigators and university administrators. The ACD working group also is selecting a series of science liaisons to further enhance outreach to stakeholders (IC Directors recently were asked for nominations).

The SCWG has completed a summary of the analysis of peer review literature, and has been analyzing other agency approaches (e.g., National Science Foundation [NSF], Department of Energy, Department of Defense, other countries) as well. The SCWG also will be consulting with psychometrics experts to gain a better understanding of the models being proposed and considered and how they may be influenced by psychometric dimensions. IC Councils and other NIH groups will be updated this fall.

Dr. Tabak explained that the diagnostic phase of this effort will end in December of 2007 when the ACD working group and SCWG issue reports. NIH leadership will consider input from the RFI and both working groups and then determine next steps, including pilots to determine whether certain interventions can be designed to overcome or enhance the elements that have been identified during this diagnostic phase. The goal is to initiate these pilot activities and their associated evaluations in early spring of 2008. Based on the success or failure of these pilots, an implementation plan will be developed and the NIH, IC Councils, scientific societies, trade press, advocacy organizations, and legislature will be briefed. A subset of successful pilots will be expanded, and ultimately will lead to the development of new NIH peer review policy.

Dr. Tabak shared some emerging ideas in select categories, noting that these concepts are not in any priority order, and is not an indication of what the NIH plans to do. These ideas represent a sample of approximately 20% of the 2,500 responses to the RFI as well as other comments. Dr. Tabak encouraged Council members to provide additional input.

**Review Criteria and Focus/Application Structure.** Dr. Tabak noted that many have discussed the issue of whether one “reviews the project versus funds the person.” Some have argued that there should be a streamlined review for experienced, highly successful investigators (drawing upon, for example, the experience in the IRP where there is more emphasis on retrospective versus prospective review). However, the argument against this approach involves concerns that it might present barriers to less experienced investigators. Many also have argued that there should be separate application modes and review criteria for those subsets of highly innovative ideas for which there is no precedent.

**Reviewer Mechanisms/Mechanics.** Dr. Tabak indicated that there has been a fair amount of input suggesting that the NIH refocus study section discussions on the strengths of applications and not their weaknesses. Different models of review have been discussed. One example is an “editorial board” model, in which there is a two-stage review. Electronic review also has been discussed, as has allowing applicants to ask questions and correct factual errors through some type of discourse or dialog between the applicant and the reviewers. Many individuals suggested having different types of review for different types of science; others have asked whether different types of reviews should be used for new investigators and/or for clinical research. Dr. Tabak noted that the NIH as a whole has funded less than 10% of AOs; because clinical trials tend to be AOs, is the NIH unduly biasing itself against these types of trials? There also has been a call for interdisciplinary research; however, at a time when study sections are considered to be

too large already, this appears to be diametrically opposed to including an interdisciplinarity component to the review. Dr. Tabak suggested that a two-stage review might help overcome this issue. With regard to SBIR/STTR applications, input was received about whether academics are the right people to be reviewing small businesses.

Dr. Tabak noted that some of the feedback indicates that there is support for a “chicken in every pot” approach to science, in which the first application that gets funded is the investigator’s first and primary grant. That investigator’s subsequent applications could then have their priority scores multiplied by increasing factors. He explained that many have argued in favor of providing more useful feedback to new investigators and including a clearer ranking to those applications that are unscored. Dr. Tabak noted that study section members have suggested instituting a pre-application to provide rapid identification and separation of competitive from non-competitive ideas and meaningful advice to A0 applicants.

**Reviewers and Review Culture.** Maximizing review and reviewer quality is a key point for councils to consider. How much contextual information should reviewers be provided, or is that the purview of the National Advisory Councils? Dr. Tabak indicated that input received and analyzed to date includes an emphasis on the need for training for new reviewers as well as continuing education for established reviewers and Science Review Administrators (SRAs). Other suggestions include providing incentives for reviewers, mandatory and/or more flexible service on study sections, increased support for reviewers, rating the reviewers and SRAs, having more reviewers per application, and anonymizing the process (as is done at NSF). Dr. Tabak noted that there also were suggestions that reviewers be more fully identified. Other input promoted the idea of enhancing the reviewers’ experience by having the panel participate in one “fun” activity unrelated to the review and advanced the concept of holding the review meetings at locations across the country.

**Scoring Issues.** Dr. Tabak explained that comments in this area suggested that the NIH “overcome the perils of percentiles,” and that too many strong applications in a “hot” area of science favors orthodoxy. Many have proposed that at the end of the review, the study section should go back through each application and rank them to ensure that the score received on the first day of the review is the same as the score received on the second day. Others have recommended including additional dimensions to extract more information and provide better feedback to applicants and program staff. For example, a two-score system could be employed. Dr. Tabak commented that applicants become upset when they receive a score on their application, do everything indicated on the summary statement, resubmit, and still receive the same score. The same score could be given to the resubmitted application because there was a new review team that identified different concerns, or during the first review, the review team was hesitant to inform the investigator that his or her proposal was not good. Reviewers are often loathe to be too critical—Dr. Tabak noted that it is easy to criticize little items on an application, but often difficult to inform someone that their idea is a bad one. Two scores might be one approach to resolving this issue.

**Other Issues.** Dr. Tabak explained that one suggestion was to limit the percent effort that can be recovered on grants for Principal Investigators. There also were other comments related to indirect cost rates (which, he said, are far too high in the opinion of some).

## Discussion

Dr. Katz asked about the concept of two scores, which was reacted to negatively by NIAMS program staff at an internal meeting. He noted that Dr. Antonio Scarpa, CSR Director, offered NIAMS the opportunity to engage a two-score system as a pilot activity. Dr. James Weinstein, Professor and Chair of the Department of Orthopaedics at Dartmouth-Hitchcock Medical Center and a member of the Council, explained that one issue is determining how to provide appropriate feedback that can be actionable without leading to total disappointment on the part of the investigator. There is a dilemma caused by investigators perceiving that if they incorporate actionable feedback, they will receive a positive response 6-9 months later, only to find out that is not the case. He expressed enthusiasm for the "editorial board" concept of review, and suggested that it would provide applicants with more definitive answers.

Dr. Rosen voiced his support for the concept of having a pre-review, such that junior or new investigators send their application in to "test the waters" to get a better idea of their prospects. He noted that study sections are seeing 95-125 grants per session, with a limited number of reviewers and fewer senior investigators serving as reviewers. These have been chronic problems—if some of the applications can be screened out the scenario is presented such that it is not considered "triage versus not triaged," but rather a pre-review, it would be extremely helpful. Dr. Rosen added that a lot could be done on a pre-review, whether it is handled by the Chair of a study section or by a group of people who might volunteer to provide editorial comment. Overall, the load has to be reduced in study sections, and the number of competent senior reviewers has to be enhanced. Dr. Tabak indicated that the ratio of applications to qualified reviewers is a key parameter, and anything that can be done to appropriately reduce the number of applications while at the same time enhancing the situation so that there are more qualified reviewers participating will improve the overall situation. Dr. Rosen added that one could envision having a group of senior investigators who do not want to serve on study sections but are able to serve as editorial reviewers for new applications to provide comments, perhaps in a mentoring-type scenario.

Dr. Katz noted that the orthopaedic community is well-suited to review new investigators, with the inclusion of mentors at other institutions who conduct a pre-review. Dr. Jacobs explained that through the U.S. Bone and Joint Decade, there are grant writing workshops and an ongoing program of having mentor-mentee relationships established at these grant writing workshops. The program includes followup with the mentors in which mentees submit either foundation or federal grants for comment to the mentor prior to submission to the agency.

Dr. Raisz noted that the problem of peer review has become extremely daunting. He explained that most of his colleagues do not want to serve on study sections because the load is far too large, the rewards are far too small, and the overall system needs to be fixed. In the past, there was not a prevailing feeling that so few people got funded, the load was smaller and the number of people on study sections was smaller, which made for collegiality and function. An approach to increasing the rewards and decreasing the pain of study section function must be devised to get more people back into the system and make it something that people want to do.

Dr. Kathleen Green added that the concept of an editorial board is an interesting one. She asked about the possibility of combining some of the functions of an editorial board within the CSR structure to provide some consistency to the review process. Dr. Tabak noted that anything that could increase the stability of the review pool also provides enhancement and would be worthwhile.

Dr. Uitto commented that the entire concept of the study section as it exists today may need to be reconsidered. It might not be necessary to have people travel to the Washington, DC, area to review grants that sometimes are outside of their respective areas of expertise. A manuscript peer review process might be a viable alternative, in which those who want to travel can, but those who do not want to travel do not have to do so. This process could include a control, such as a section coordinator, and have the triage up front before applications go through this process. Dr. Katz reminded Council members that approximately 10% of applications will be reviewed electronically this year. Dr. Tabak added that electronic review may become the stand-alone approach, or a hybrid model may be created. Overall, there are definite ways to position electronic review to add value.

Dr. Hahn commented that there is a problem with a very small number of people voting on a grant and the study section not having expertise in that particular area. She expressed enthusiasm for the journal idea, so that for every grant there is an *ad hoc* committee of reviewers with the appropriate knowledge who do everything electronically, with inclusion of a control mechanism such as a section editor who has a broader view to avoid perpetuating the same idea (which, she said, can be a problem when there is a small number of reviewers in a small specialized area). This approach would cut down on the amount of travel, and could be coupled with a reward mechanism of some type (e.g., some type of guarantee that a grant would be funded longer). She indicated that another problem with the system as it exists today is that the study section in which a reviewer participates cannot review proposals from that reviewer. Therefore, it is often the case that the individuals who know the most about a reviewer's area of expertise cannot review his or her applications.

Council member Dr. Martin Kushmerick, Professor in the Department of Radiology at the University of Washington, voiced enthusiasm for having the reviews emphasize the strengths and other positive aspects of applications. He indicated that oftentimes applicants are discouraged and left with a feeling that their application is being reviewed by a competitor who does not want to see them get funded.

Dr. Serrate-Sztein asked about the concept of introducing psychometrics to the review process, including the analysis of applications and the voting patterns of reviewers. She asked if Dr. Tabak and colleagues received any suggestions on defining what a "minimally important" difference would be. Dr. Tabak responded that this issue has been the focus of a great deal of attention. He explained that many in the community feel that differentiating between a score of 1.34 and 1.35 approaches scientific disingenuousness. One suggestion may be to use integers only. At an extreme, binning and other approaches could be used, but this may provide too much ambiguity and could shift an inappropriate amount of responsibility on the shoulders of program staff. A balance needs to be struck between the peers providing the review and giving enough information. Dr. Tabak added that humans tend to want to have the choice between seven

categories—seven appears to be a “magic number,” such that more choices other than just “high,” “medium,” and “low,” are needed—variance is needed to encompass seven categories. He also commented that many complain about not enough being done to promote innovation. He suggested that it may be possible to utilize a matrix score whereby one of the dimensions is innovation. Depending on the needs of the Institute, that domain could be weighted higher or lower depending on what the needs are. Public health could be another weighted dimension. Psychometric experts indicate that one must be true to what is truly statistically relevant, but that one must also be able to extract the specificity necessary for decisionmaking.

## VIII. SBIR/STTR WORKING GROUP REPORT

Dr. Joan McGowan noted that this session was a direct continuation of the presentation given at the last Council meeting, which included a summary of the discussions from the April 2007 scientific retreat at which NIAMS staff discussed the Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) mechanisms. At the last Council meeting, Ms. JoAnne Goodnight, who coordinates the entire SBIR/STTR program across the NIH, also gave a presentation with additional information in these initiatives. Dr. McGowan reminded Council members that these two mechanisms are mandated by law; there is a substantial set-aside for each, whereby 2.5% of the NIH extramural research budget is allocated to SBIR, and 0.3% goes to STTR. Dr. Katz commented that current legislation on the Senate side is pushing for a substantial increase in these percentages.

Dr. McGowan explained that the NIAMS SBIR/STTR Working Group included NIAMS Council members as well as NIAMS staff. The Working Group was given the following charge by Dr. Katz: Explore the scientific areas that may be targeted to request applications from the small business community. The Working Group considered the following discussion questions:

- Which NIAMS scientific areas are ripe for small business research?
- How can those opportunities best be targeted?
- Can NIAMS SBIR/STTR plans be tied to other initiatives driven from the NIAMS long-range plan or recent NIAMS Retreat and Planning Panel topics?
- Should small business audiences be targeted at national scientific meetings to advertise NIAMS' interest?

Dr. McGowan noted that the NIH convenes an annual SBIR meeting at which there are opportunities for program staff to meet with small businesses. NIAMS SBIR/STTR Program coordinator Mr. Elijah Weisberg will be attending these annual meetings to network with these businesses and explore the potential for utilizing these mechanisms in areas of interest to the Institute.

Reauthorization of the SBIR/STTR program is under consideration in Congress. Ms. Goodnight gave a presentation to Congressional staff focusing on how these programs currently are being

managed. She highlighted some of the innovations ongoing at the NIH, such as the Pipeline to Partnership Program, which involves “matchmaking” between small business partners with more strategic business partners and investors to facilitate the commercialization of awardee products and technologies.

The Working Group looked at current NIAMS focus areas relative to the number of incoming SBIR/STTR applications in each. Those areas include treatments (23 applications), diagnostics (9), devices (4), implants (6), tissue engineering (4), and computer software/simulations (5). Dr. Kathleen Green explained that the Working Group reviewed these data and in further deliberations, developed the following draft list of suggested areas to target:

- Clinical Trials
  - Metrics for pain, inflammation
  - Biostatistical and bioinformatics support.
- Assays
  - Standardized assays for antibodies and cytokines
  - Multiplex assays for biomarkers
  - Nanotechnology for serum cytokines
  - Standard extracellular matrix substrates and media for specific cell types (e.g., epidermal raft cultures *in vitro*).
- Drug Delivery
  - Nanotechnology for cutaneous drug delivery
  - Improvements to delivery of DNAs, oligos, and peptides into cultured (cutaneous) cells (keratinocytes in particular)
  - Local drug delivery systems for bone growth factors.
- Treatment
  - Novel approaches for treating hyperpigmentation (due to cuts, burns, acne) and other ethnic-related issues.
- Diagnostic Tools
  - Molecular diagnostics for musculoskeletal sepsis, neoplasms, and other inflammatory diseases affecting the musculoskeletal system
  - Needle with a microarray chip for *in vivo*, *in situ*, in tissue gene expression profiling, including multiple sites in the same tissue
  - Develop a biopsy needle for obtaining soft tissue and muscle dialysates
  - Develop microarray technology to distinguish infection versus flare in lupus.
- Imaging Bioinformatics Tools
  - Tools and methods for the analysis of complex imaging (data from the Osteoarthritis Initiative).
- Orthopaedics and Bioengineering
  - Tissue-engineered medical products (bone, cartilage, muscle, ligament, tendon)

- Novel bearing surfaces for artificial joints
  - Implant surface nanotexturing for hard and soft tissue fixation
  - Implantable sensor technologies, including joint telemetry
  - Biomarkers of periprosthetic osteolysis and orthopaedic implant failure
  - Immunological profiling of orthopaedic implant recipients
  - Development of robust joint simulators, including the axial and appendicular skeleton.
- Educational Materials
    - Develop courses on informatics
    - Provide multilingual editions of patient information brochures
    - Encourage research teams to put research results into products for use by the public (exercise videos, etc.)
    - Educational materials for skin conditions specific to ethnic populations (e.g., that solar damage is a big issue but underappreciated by those with dark complexions, etc.).

To follow up on these ideas, Dr. Kathleen Green noted that the Working Group made the following suggestions: (1) convene focus groups of scientists and business people at national scientific meetings to discuss unmet needs in the context of potential business opportunities in NIAMS-related mission areas, (2) perform outreach to small businesses with established core capabilities to determine if these capabilities can be applied to NIAMS research areas, (3) include small business in NIAMS-wide solicitations if appropriate, and (4) prepare an SBIR/STTR solicitation in one or more priority areas. Dr. Green also noted that it might be beneficial to leverage interactions or partnerships not just with small businesses, but with individuals who have diverse expertise and use NSF and other IC funding to leverage resources to an even greater extent.

## **Discussion**

Dr. Katz noted that there are opportunities for NIAMS program staff to meet with small business communities at the NIH-led meetings to see what opportunities might exist. He asked whether small businesses were involved in making the suggestions proposed by the Working Group, and whether these entities would still retain their small business status if they successfully participated in the program. He also asked if there were small businesses already participating in the areas proposed by the Working Group. Dr. Jacobs explained that there are a number of small businesses involved in these topics, particularly in innovative areas such as the spine, novel coatings and surface treatments, etc. It is their goal to develop a marketable product and then be bought out by a larger concern. He added that many of the innovative advances in medical technology do not come from large companies, but rather from small, start-up businesses.

Dr. Raisz noted that the SBIR activities often contain methods or new concepts that a young investigator working in a certain area might find very useful in his/her own research. He added that access to what the SBIR awards are and understanding of what those opportunities are has not been optimal. Creating some way of highlighting that they are out there and indicating both to the businesses and to NIAMS investigators that these interactions are worthwhile, would advance this program and make it more desirable and accepted by the academic community. Dr. Parr added that most of the large companies today in the medical device field look to the small

start-up companies that are carrying out the innovative development of new technologies up to the point of proof-of-principle. If these small businesses can get through FDA clearance, it enhances their buy-out value tremendously. The difficulty lies in picking a “winning” technology, so there is some degree of risk, he cautioned.

Dr. Kotzin asked whether the value of the small business awards in terms of what has happened to the technology and whether it has led to larger advances has been evaluated. Dr. Katz indicated that there are data on the outcomes of SBIR awards. At a previous Council meeting, NIH-wide data were presented that were very positive in terms of the “success” of the SBIR program, with 38-40% of applications being considered successful. Dr. Parr added this measure depends on the definition of success. The success rate for true commercial products coming from the NIH SBIR program is at about 17%, based on scientific publications. This information is difficult to track, because the NIH is not made aware of instances when a small business’ technology is sold to a larger entity. Dr. Katz commented that millions of dollars have been spent in this area. Of the \$11 or \$12 million spent by the NIAMS in this area, the Institute is able to fund much more highly rated applications than in many other areas because it is focused heavily in engineering, particularly in the skin and orthopaedic areas. There appears to be an opportunity to use some of these awards to help the Institute address some of its major areas of focus.

Dr. Scalettar asked about what happens once these companies achieve success and whether there is a return on the investment to the sponsoring IC. Dr. Katz explained that the program is intended to increase the scientific productivity of the country and help stimulate the economy. The program represents a national commitment to enhancing the biomedical industry. In terms of next steps, Dr. Katz indicated that he plans to charge the Working Group, with more program staff, to identify some of NIAMS’ areas of focus and determine whether there is a response from the small business community in an open competition format. Dr. McGowan noted that areas will be selected in which it is already known that there are small businesses that have the requisite expertise and capabilities.

A motion was made, seconded, and approved for NIAMS to pursue an initiative to focus requests for small businesses in areas of interest to the Institute.

#### IX. BSC REPORT

This report was presented in closed session.

#### X. FY2009 INITIATIVES

A discussion on FY2009 initiatives was held during closed session.