National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

February 3, 2009

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

MINUTES OF THE 67th MEETING

February 3, 2009
8:30 a.m. to 3:00 p.m.

I. CALL TO ORDER

The 67th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on February 3, 2009, 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
Ms. Carmen Cheveres (by telephone)
Dr. Leslie Crofford
Dr. Betty Diamond
Ms. Karen Evans
Dr. B. Lee Green
Dr. Kathleen Green
Dr. Joshua Jacobs
Dr. John H. Klippel
Dr. Henry Kronenberg
Ms. Ann Kunkel
Dr. Clifford J. Rosen
Dr. H. Lee Sweeney

Council members not present:
Dr. Kevin Campbell
Dr. Linda Griffith
Dr. Robert J. Oglesby (*Ex Officio*)
Dr. James Weinstein
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
Ms. Justine Buschman
Dr. Robert Carter
Mr. Richard Clark
Ms. Stephanie Craver
Ms. Wilma Peterman Cross
Ms. Robin DiLiello
Ms. Teresa Do
Dr. Jonelle Drugan
Mr. Erik Edgerton
Ms. Sharon Fair
Ms. Barbara Footer
Dr. Mark Gourley
Ms. Gail Hamilton
Ms. Kim Holmes
Mr. Andrew Jones
Dr. Stephen Katz
Ms. Valeri Kim
Dr. Gayle Lester
Dr. Helen Lin
Ms. Anita Linde
Ms. Mimi Lising
Ms. Leslie Littlejohn
Dr. Kan Ma
Dr. Marie Mancini
Ms. Leslie McIntire
Dr. Joan McGowan
Ms. Regina Mong
Ms. Melinda Nelson
Ms. Anna Nicholson
Mr. Kwame Nkrumah
Dr. Glen Nuckolls
Dr. John O‘Shea

Dr. James Panagis
Ms. Natalie Reyes
Ms. Trish Reynolds
Dr. Louise Rosenbaum
Ms. Karin Rudolph
Dr. Susana Serrate-Sztein
Ms. Sheila Simmons
Ms. Theresa Smith
Ms. Allisen Stewart
Ms. Yen Thach
Dr. Phil Tonkins
Dr. Hung Tseng
Dr. Bernadette Tyree
Ms. Marcia Vital
Dr. Fei Wang
Dr. Yan Wang
Dr. Chuck Washabaugh
Mr. Elijah Weisberg
Ms. Sara Rosario Wilson
Dr. James Witter

Guests

Mr. Michael Bykowski, Consolidated Solutions and Innovations
Ms. Ann Elderkin, American Society for Bone and Mineral Research
Dr. David Fox, American College of Rheumatology (by telephone)
Ms. Christy Gilmour, American Academy of Orthopaedic Surgeons
Dr. Roger Glass, Fogarty International Center, NIH (by videoconference)
Mr. Rick Hansen, Digicon Corporation
Dr. Michael Johnson, Fogarty International Center, NIH
Ms. Amy Melnick-Scharf, Arthritis Foundation
Dr. Aron Primack, Fogarty International Center, NIH
Mr. Chris Rieser, National Psoriasis Foundation
Dr. Nelson Sewankambo, Makerre University (by videoconference)
Mr. Stephen Spotswood, U.S. Medicine, Inc.

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept with no changes the minutes of the 66th Council meeting, held on September 23, 2008.

III. FUTURE COUNCIL MEETING DATES

Future Council meetings are currently planned for the following dates:

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 by acknowledging and thanking Dr. Susana Serrate-Sztein, Director of the NIAMS Division of Skin and Rheumatic Diseases, who served as the Council's Acting Executive Secretary for the meeting. Dr. Katz invited attendees to review the NIAMS ShortTakes online, which include more details on many of the topics covered in his report. He noted that his "Director's Column" focuses on the NIAMS Long-Range Plan, which was discussed later in the meeting.

Introduction of New Council Members

Dr. Katz welcomed the following four new Council members:

- Dr. Leslie Crofford, Chief of the Division of Rheumatology and Professor in the Department of Microbiology, Immunology, and Molecular Genetics at the University of Kentucky. Dr. Crofford also serves as the university's Director of the Center for the Advancement of Women's Health.

- Karen Evans, Executive Director of the Will and Jada Smith Family Foundation, a private organization dedicated to the improvement of the lives of youth and their families in Baltimore, Philadelphia, and Los Angeles. Ms. Evans is also the Chair of the Board of Directors of the Lupus Foundation of America.

- Dr. Linda Griffith, Director of the Biotechnology Process Engineering Center and a Professor of Mechanical and Biological Engineering at the Massachusetts Institute of Technology, Cambridge. Dr. Griffith is an expert in the fields of tissue engineering and regeneration, and in the development of biomaterials. Dr. Griffith was unable to attend this Council meeting.

- Dr. Henry Kronenberg, Professor of Medicine at the Harvard Medical School and Chief of the Endocrine Unit at Massachusetts General Hospital, Boston. Dr. Kronenberg is a member of numerous professional associations, including the Endocrine Society, the American Society for Bone and Mineral Research, and the International Bone and Mineral Society.

Recent Awards

Dr. Katz reported that 12 NIH-supported researchers, including NIAMS-grantee Dr. James Iatridis of the University of Vermont, recently received the Presidential Early Career Award for Scientists and Engineers (PECASE) for his research on engineering for the prevention of intervertebral disc degeneration. The PECASE is the Nation's highest honor for scientists at the outset of their professional careers. At the American College of Rheumatology/Association of Rheumatology Health Professionals' (ACR/ARHP) Annual Meeting, Dr. Janet Austin, Director of the NIAMS Office of Communications and Public Liaison, was honored with ARHP's 2008 Addie Thomas Service Award. The award recognizes "individuals who have been an active volunteer involved with local, regional, and national arthritis-related activities." In addition, Council member Dr. Betty Diamond, Chief of the Laboratory of Autoimmune Diseases at the Feinstein Institute of Medical Research, was recently honored by the Lupus Foundation of America with the Evelyn V. Hess Research Award for her lifetime of achievements in lupus research.

Update on Budget and Congressional Activities

Dr. Katz commented that Congress and the new Administration have made funding science a priority in their recent efforts to stimulate the economy. It has been argued that the funding of science, and biomedical/health research in particular, would create jobs, spur the creation of innovative technologies, reduce health care costs, and provide a foundation for future industry.

In Fiscal Year 2008 (FY08), the NIAMS funded 253 new and competing continuation applications for a success rate of 20.9 percent; a figure slightly higher than last year's rate of 20 percent. The Institute's payline was at the 15th percentile. The overall NIH success rate was 21.8 percent. Additional details about the distribution of the FY08 appropriation, including success rates for all budget activities, are available on the NIAMS Web site.

For FY09, a continuing resolution (CR) is in effect to fund most of the government until March 6, 2009. The funding level for NIAMS under the CR is $508.6 million, which is essentially level with the FY08 budget without the supplemental funds that were awarded last year. An interim funding plan has been developed for operations under the CR and is available on the NIAMS Web site. Specific funding policies for FY09 will not be known until all of the appropriations bills have been passed. In the meantime, support for new investigators remains an important NIH goal. The emphasis will be less on reaching a numeric target and more on striving to have comparable success rates for new applications submitted by new and established investigators.

Dr. Katz explained that a second NIH-wide new investigator emphasis area is increasing the numbers of early stage investigators (ESIs). An ESI is an individual who is within 10 years of completing the terminal research degree or within 10 years of completing medical residency/fellowship, who fits the new investigator definition. The NIH recently established the ESI designation to encourage researchers in their early careers to transition to independent careers more rapidly and receive an R01 award earlier.

The President's Budget request for FY10 is anticipated in the near future. Details will be provided on the NIAMS and NIH Office of Budget Web sites as soon as they become available.

On January 15, 2009, the NIH released the Research, Condition, and Disease Categorization (RCDC) system—a new and different way to categorize and report the NIH research portfolio. The RCDC includes 215 historically-reported research categories covering grants data, interagency agreements, contracts, and intramural research projects. The RCDC system uses knowledge management and provides, for the first time, complete project listings and associated dollars for each category. Dr. Katz noted that there will be differences—in some cases big differences—in terms of what the RCDC system outputs this year compared with similar information generated by NIH Institutes and Centers (ICs) in previous years.

During the 110th Congress, members introduced numerous bills on topics of great interest to the NIAMS. It is expected that many of those bills will be reintroduced during the 111th Congress; the Institute will continue to update Council members on this legislation. Dr. Katz reported that Title VIII of the Food and Drug Administration Amendments Act of 2007 has passed and expands the scope of trials that are required to be registered in ClinicalTrials.gov, and mandates the submission of summary results for many of those trials. Under the law, NIH grant awardees (including those with Cooperative Agreements) may be responsible for registering their trials and submitting trial summary results to ClinicalTrials.gov. The NIAMS is in the process of sending a notice to all grantees who are affected by this policy, to clarify their reporting responsibilities and urge compliance with the registration and results reporting requirements. At the September 2008 Council meeting, Dr. Katz reviewed the Comparative Effectiveness Research Act of 2008, which would establish a nonprofit corporation, the Health Care Comparative Effectiveness Research Institute, to contract with appropriate federal agencies or the private sector to conduct comparative effectiveness research. The new administration is very interested in promoting comparative effectiveness studies as part of its overall efforts to reform the health care system and related costs; the NIH will undoubtedly play a key role in this arena, providing information to help shape policy decisions. On August 9, 2001, President Bush announced that no federal funds could be awarded for research using human embryonic stem cells unless certain criteria were met. President Obama has signaled his support for lifting those restrictions, making it possible for the NIH to fund additional research in this area.

Highlights of Selected Recent Scientific Advances

Extramural Research

- Dr. Gerard Karsenty, who has funding from both the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIAMS, published a highly publicized study that is changing the understanding of bone biology and its connection to other organ systems. Although serotonin is known mainly as a neurotransmitter in the brain, it also is produced by the duodenum. Dr. Karsenty and colleagues found that this gut-derived serotonin inhibits bone formation in an Lrp5-dependent manner (Lrp5 is a gene thought to be responsible for controlling osteoblasts). This finding opens the door to new therapies that can increase bone mass (*Cell.* 2008 Nov28:135(5):825-37).

- Dr. Roland Baron and colleagues have identified a protein known to increase bone mass that also influences energy metabolism, delta-FosB. Although connections between obesity and diabetes are well-recognized, links between energy metabolism and bone metabolism have only recently emerged. The researchers found that mice that overexpress delta-FosB in the bone, fat, and brain, for example, show a marked increase in bone mass and a significant decrease in fat mass. Because delta-FosB is produced in brain as well as bone and fat, it is possible that the changes in energy metabolism reflect signals originating in the brain (*Endocrinology.* 2008 Sep 4 [Epub ahead of print]).

- Dr. Bess Dawson-Hughes and collaborators have determined that men and women who took bicarbonate supplements excreted lower levels of bone loss markers than those who took potassium chloride supplements or a placebo. In a relatively short-term (84 day) study, four dietary supplements were used; the investigators found that the net acid secretion decreased by more than 30 percent and the calcium loss in the urine was reduced in the bicarbonate supplement groups (*J Clin Endocinol.* 2008 Oct 21 [Epub ahead of print]).

- Council member Dr. James Weinstein and colleagues have produced many interesting papers stemming from the Spine Patients Outcomes Research Trial (SPORT). Two of these recent papers focus on patient preference for surgical repair of lumbar disc herniation linked to concerns about nonoperative treatment and on cost effectiveness of surgery versus non-operative approaches. These trials are affecting the treatment and approach to these patients. One of Dr. Weinstein's goals is to embrace patient choices with regard to decision-making in terms of surgical and non-surgical approaches (*Spine.* 2008 Nov 15;33(24):2663-8

- Dr. Kevin Campbell and colleagues published a paper on mechanisms and possible treatment for exercise-induced fatigue in muscular dystrophy and other myopathies. With his colleagues, Dr. Campbell (a member of the Council and Director of the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center) determined that defective neuronal nitric oxide synthase (nNOS) localization is responsible for extreme, debilitating fatigue after even mild physical exertion in muscular dystrophies (*Nature.* 2008 Nov 27;456(7221):511-5).

- A potential new biomarker for rheumatoid arthritis has been identified by Dr. Lundberg and colleagues from the Imperial College of London and the University of Nebraska. Working collaboratively the investigators explored the antibody response to alpha-enolase seen in RA patients and discovered a citrullinated alpha-enolase peptide, CEP-1, which was specifically recognized by antibodies from RA patients (*Arthritis Rheum.* 2008 Oct;58(10):3009-19).

- Two recent articles discuss the payoff of genome-wide association studies. Many NIAMS grantees worked together on these projects, which included two large multinational studies involving many of the centers that the Institute supports. One study involved 5,000 patients and 5,000 controls; the other used 3,000 patients and 3,000 controls. In the larger study, researchers confirmed the association of HLAC and three other genes involved in the IL-23 signaling pathway. The smaller study discusses the association of quantified envelope genes, LCE3b and LCE3c, with the immune system and the epidermal products system (*Nature Genetics.* 2009 Feb;41:199-204 and *Nature Genetics.* 2009 Feb;41:211-15).

- Dr. David Rubenstein and colleagues used a mouse model of pemphigus foliaceus (PF) to demonstrate that the protein p38 mitogen-activated protein kinase (p38 MAPK) is modified and activated in the skin of mice with the disease. These NIAMS-supported researchers found that mice pretreated with a p38 MAPK inhibitor before injection with human PF antibodies did not develop skin blisters, indicating that inhibition of p38 MAPK can prevent the formation of blisters induced by PF autoantibodies (*Am J Pathol.* 2008 Dec;173(6):1628-36).

Intramural Research

- Drs. Paul Plotz (Chief of the NIAMS Arthritis and Rheumatism Branch) and Nina Raben published work on unmasking disordered recycling within muscle cells in patients with Pompe Disease. They found that the cell's recycling centers, or lysosomes, were filled with glycogen which could not be digested, causing a backup of waste. This is one of the reasons that simply replacing the enzyme is not effective in these patients (*Hum Mol Genet*. 2008 Dec 15;17(24):3897-908).

- Dr. Rocky Tuan, Chief of the NIAMS Cartilage Biology and Orthopaedics Branch, and colleagues recently discovered that medical waste contains progenitor cells that feature many of the same differentiating properties as adult stem cells. Waste tissues are typically removed from orthopaedic injuries during surgery to promote healing, including those from war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells (*J Bone Joint Sur [Am]* 2008 Nov; 90(11):2390-8).

- A study was published by researchers from the NIH Chemical Genomics Center that describes the activity and discusses the mechanisms by which the drug PTC124 increases the signal from firefly luciferase in cellular assays in ways independent from the drug's expected action of overcoming nonsense mutations by stop codon read-through. Patients and family members that are associated with the trials may be confused by this new finding, and some might interpret the paper as challenging the data that led to the development of this drug. This new publication does recommend caution among researchers conducting screens of molecular libraries using a single reporter, but any impact of these findings on the current clinical trials of PTC124 are unclear (*PNAS. Epub* Feb 2, 2009).

Personnel Changes at the NIH and NIAMS

Dr. Katz announced that Dr. Raynard Kington, NIH's Deputy Director since February 2003, is now the Acting NIH Director, while Dr. Lawrence Tabak is the Principal Acting Deputy Director for the NIH. Dr. Tabak has been the Director of the National Institute of Dental and Craniofacial Research since September 2000. In December 2008, Dr. Linda Birnbaum was appointed as the new Director of the National Institute of Environmental Health Sciences. Dr. Birnbaum joins the NIH from the Environmental Protection Agency's Office of Research and Development. In the Office of Extramural Research, Dr. Sally Rockey is serving as the Acting Deputy Director of Extramural Research until a permanent appointment is made. As required by the NIH Reform

Act of 2006, the NIH has established a Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI). Dr. Lana Skirboll, Director of the NIH Office of Science Policy, is now the Acting Director of the DPCPSI.

At the Institute level, Dr. Dan Kastner, Clinical Director of the NIAMS Intramural Research Program, has been tapped by the NIH Deputy Director for Intramural Research to play a leadership role in facilitating clinical research across the NIH. Dr. Hung Tseng has joined NIAMS Extramural Program as Director of the Extracellular Matrix Biology and Diseases Program in the Division of Skin and Rheumatic Diseases. The Institute is currently recruiting a permanent Director for the Division of Extramural Research Activities (DERA). Ms. Melinda Nelson has agreed to serve as the Acting Director, DERA, as of February 1, 2009, while the search is ongoing. Dr. Katz thanked Dr. Glen Nuckolls of NIAMS' Division of Musculoskeletal Diseases, who has been serving as Acting DERA Director since June.

NIH/NIAMS Activities and Plans for the Future

Dr. Katz provided an update on NIH efforts to improve its peer review system. These activities have included efforts to:

- Reduce administrative burden.
- Fund the best science earlier.
- Eliminate A2 applications.
- Ensure fair reviews across career stages in scientific fields.
- Modify the NIH new investigator policy to identify early stage investigators.
- Cluster applications in review so that early stage investigators will be reviewed together in a particular study section.
- Improve the quality and transparency of the reviews.
- Implement the core criteria and 9-point rating scale.
- Base the overall impact score on core and additional criteria.
- Provide the core and overall impact scores for streamlined applications to applicants.
- Engage the best reviewers.
- Give new reviewers additional flexibility in terms of their tenure of duty.
- Assess the feasibility of virtual reviews.

Dr. Katz reported that the NIH and the National Aeronautics and Space Administration continue to work on the funding opportunity announcement he described at the September 2008 Council meeting. Dr. Joan McGowan, Director of the NIAMS Division of Musculoskeletal Diseases, is leading a team of Institute staff who are developing this initiative, on behalf of the NIH.

In December 2008, more than 3,000 national and international clinicians, researchers, policy makers, and community leaders attended the NIH Health Disparities Summit. This enormously successful event was run by the National Center for Minority Health and Health Disparities. The purpose of the meeting was to highlight recent progress made in addressing health disparities and to redefine the agenda for health disparities research. Dr. Katz moderated a session on Health Disparities and the Intersection of Science, Policy, and Practice at the Summit.

Dr. Katz briefly discussed the NIH Global Health Report, noting that the NIH is examining its engagement and investments in international biomedical research and global health. Institute and Center (IC) Directors discussed the topics at their 2008 Leadership Forum, and the NIH is organizing a 1-day retreat to enable ICs to share information and perspectives on international program strategies, common obstacles, and innovative program models.

With regard to NIAMS-specific activities and plans, Dr. Katz provided additional information on the Building Interdisciplinary Research Teams (BIRT) supplements as a followup to the presentation given at the last Council meeting. The first 11 BIRT awards have been made from a pool of 27 applications; the RFA has been issued for this year. Also at the last Council meeting, members were informed of NIAMS' plan to consider, on an expedited basis, applications for ancillary studies to large clinical trials. With input from the Council, the Institute is moving forward with this effort.

NIAMS continues to examine its training grant and career development program. In 2007, the Institute completed an outcome evaluation focused on the success of its T32, F32, K01, and K08 mechanisms. A working group of outside experts considered these programs to be successful in maintaining a highly trained workforce and provided 10 recommendations for the Institute's consideration. The Institute has been able to address some of these recommendations; NIAMS Deputy Director Dr. Robert Carter has been asked to continue to examine the Institute's training program in more detail. Currently, he is working with a team of NIAMS staff to take a closer look at the structure and review criteria for the T32 program. Dr. Katz explained that the primary goal of the T32 program is to promote the training of individuals who will pursue careers in research related to NIAMS mission areas. The Institute has already addressed the metrics available to measure success of former trainees (job placement, publications, and funding). These metrics can be used both by review panels to determine the success of a T32 at a particular institution, and by NIAMS to judge whether its investment in the program is helping to maintain a pipeline of qualified trainees.

Before concluding his remarks, Dr. Katz highlighted some of the Institute's many dissemination efforts (several pieces of information that have recently been prepared were provided to Council members at the meeting). He also noted that the Institute is in the planning stages of a National Multicultural Outreach Initiative to improve access to research-based and culturally- relevant

health information for minority and underserved populations. More information on the initiative will be provided to the Council at a future meeting.

Discussion

Council member Dr. Joshua Jacobs, an orthopaedic surgeon at Rush University Medical Center, commented that the SPORT Trial has been worth the NIAMS investment; its results have attracted broad interest in the community. In terms of developing evidence-based guidelines, it is particularly challenging in the area of surgical treatments to compare different types of surgical approaches. Large investments such as the SPORT trial are needed for the development of these evidence-based guidelines. Dr. Jacobs also noted the importance of shared decision making and noted that Dr. Weinstein and colleagues have developed tools to help practitioners create a shared decision making model to help identify the most appropriate treatments.

Dr. H. Lee Sweeney, the William Maul Measey Professor and Chair of the Department of Physiology at the University of Pennsylvania School of Medicine and a member of the Council, explained that the drug PTC124 in clinical trial reads through premature stop codons or nonsense codons that cause disease in a number of patients, including those with Duchene muscular dystrophy and cystic fibrosis. The drug does not read through authentic termination codons. The paper referred to by Dr. Katz demonstrates that the drug and its whole class can somewhat stabilize firefly luciferase. Dr. Sweeney added that the study's investigators misinterpreted their data by not including read through and stabilization as modes of action. He emphasized that the drug is not in clinical trial because it reads through firefly luciferase premature stop codons, but rather because it does so in a number of authentic transcripts from patient cells and from mouse models. Duchene muscular dystrophy and cystic fibrosis animal models show that the drug will produce enough protein to alleviate the disease. In Dr. Sweeney's opinion, the authors dismiss the animal data and the data with authentic termination codons, misinterpret their own data and made inflammatory remarks that were pulled from the paper. In addition, Dr. Sweeney noted that the investigators contacted the non-profit organizations that sponsor the drug's clinical trial and informed them that it did not work. Overall, he summarized, the situation was handled very poorly and in his mind, irresponsibly. Dr. Katz added that to their credit, some of the NIH investigators and administrators participated in a meeting to try to address and clarify some of these concerns.

Dr. Jacobs asked about the potential impacts of the proposed economic stimulus package. Dr. Katz explained that there is a large spectrum of possibilities; the NIAMS and the NIH overall have been working to accommodate the proposed 2-year package, which may include from between $2 billion per year to $6.9 billion per year for the NIH. There are questions from legislators regarding what is expected and how these dollars will be tracked. Dr. Robert Carter noted that some of these funds may be used for "catapult grants" that would move a field forward in a way not previously possible, within 2 years. Dr. Katz also noted that there is a question of how funds could be used for comparative effectiveness research. The package also includes some funds for renovation of intramural research facilities. He added that according to economists, every dollar invested in the NIH leads to $3.50 in development.

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 in Tampa, Florida, noted that some of the discussions that took place at the NIH Health Disparities Summit affirmed the meeting message to NIH ICs to increase their focus and investment in health disparities. Dr. Katz commented that the NIAMS has significant investments in a number of areas that affect minority and underserved populations (e.g., lupus). The NIAMS is not only an Institute that deals with minority/underserved issues, but also one that focuses to a large extent on women's health issues. Many of the diseases that are of interest to the Institute affect these groups disproportionately.

Dr. John Klippel, President and CEO of the Arthritis Foundation and a Council member, asked about the RCDC data and the interpretation of its use. Dr. Katz responded that the information coming out of the RCDC system will be interpreted in a variety of ways. It is important for the NIH to respond to Congress and the public with regard to where NIH money is invested. Dr. Serrate-Sztein added that, as a result of the RCDC fingerprinting system, there has been a shift in how funding appears for the category "arthritis." It is hoped that there will be opportunities to look at this fingerprinting system to more accurately reflect what is funded under the category of "arthritis." Dr. Katz noted that there are certain NIAMS investments that are not currently included in the RCDC, but efforts are underway to address this issue (e.g., for this year, NIAMS contracts related to arthritis were not included in the RCDC; those contracts will be included next year).

V. NIAMS R21 PROGRAM EVALUATION

Dr. Nuckolls posed the following question to the Council: Should the Institute continue to participate in the NIH-wide parent R21 announcement that is set to expire on May 2, 2009? R21s are relatively small, non-renewable grants, with $275,000 in direct costs over 2 years. Applications in response to the parent R21 announcement go through the Center for Scientific Review (CSR) for review in regular study sections. Percentile scores for the R21 applications are determined from the R01 percentile base. The NIAMS has maintained the same payline for R21 and (non-new investigator) R01 competing applications. Dr. Nuckolls outlined the research goals of the R21 parent program, which include supporting studies that: may involve considerable risk but may lead to a breakthrough; may lead to the development of novel techniques, agents, methodologies, models, or approaches that could have a major impact on the field; include the unique and innovative use of an existing methodology to explore a new scientific area; and, may break new ground or extend previous discoveries toward new directions or applications.

The NIAMS has been using the R21 in various funding announcements. In January 2001, the Request for Applications titled "High Risk Arthritis and Musculoskeletal and Skin Diseases Research Award" was issued. In March 2004, this RFA was discontinued, and the Institute signed on to the NIH-wide parent R21 announcement, which was renewed in March 2006, and is expected to be renewed again in 2009. The NIAMS also uses the R21 mechanism through various Program Announcements that are focused in specific research areas. Dr. Nuckolls explained that for the purposes of Council discussion at this meeting, the focus would be on

NIAMS participation in the NIH-wide parent R21 announcement, rather than these specific research areas.

There has been an increase in R21 applications NIH-wide in the past 6 years, from almost 1,000 in 2004 to more than 5,000 in 2008 and 2009. Dr. Nuckolls explained that overtime it appears that applicants and reviewers have somewhat lost track of the primary goals of the R21 funding mechanism. There are now a number of misperceptions regarding the R21 program. These include: (1) the R21 is a good starter grant for new investigators (defined as investigators who have not yet competed successfully for an R01); (2) the R21 is intended to support studies that generate preliminary data for R01 applications in any area of research; (3) the R21 is appropriate for any project of limited cost and scope; and (4) it is easier to get an R21 because it has a small budget and requires no preliminary data.

To address these types of misperceptions, an evaluation of the R21 program was conducted by NIAMS staff. The goals of the evaluation were as follows:

- Determine whether new investigators have an "affinity" for R21s.
- Compare the success rate of R21 awards compared with R01 awards for new and experienced investigators.
- Determine whether most R21s are supporting innovative, groundbreaking research.
- Consider the decision of other ICs not to participate in the R21 parent announcement.
- Consider options for changing the use of the R21 and possible impacts of these changes.

Dr. Nuckolls explained that new investigators applying to the NIH in an area of interest to the NIAMS have a choice in terms of the type of funding mechanism they select for their application. Of 225 new investigators (self identified) who had unsolicited applications assigned to NIAMS in FY08, 137 applied for R01s, 65 applied for R21s, 17 applied for R15s, 5 applied for both an R01 and an R21, and 1 applied for both an R21 and an R15. Despite the fact that there is a more generous payline for new investigator R01s, approximately one-third of these new investigators applied for an R21. In the past 4 years, the Institute has seen an increase in the number of R21 applications, from 59 in 2005 to 181 in 2008. Between one-third and one-half of these applications came from new investigators.

Dr. Nuckolls reviewed the success rates of R21s versus R01s. In 2006 and 2007, the success rate for experienced investigators applying for R21s surpassed that of R01s or new investigator R21s. The R21s are competing with the R01s for slots on the NIAMS payline. NIAMS Program Directors that have R21s in their portfolios were asked to examine the currently active R21s in response to the NIH-wide parent R21 announcement and rate them according to how well they match the R21 mechanism criteria. NIAMS Program Directors reported that about 60 percent of currently active R21s are good matches for the type of research being sought after in the R21 program. However, there were a number of grants for that do not have the high-risk, high potential impact features associated with the R21 program. No correlation was found between

how well the R21 applications scored in study section versus how well Program Directors felt they matched the mechanism criteria.

Dr. Nuckolls referred to this discrepancy as "the reviewers' dilemma." If a reviewer is enthusiastic about the scientific merits of an R21 application, should he/she adjust the score because it is not likely to have a major impact or lead to a breakthrough? Despite the special intent of the R21 program, applications are not currently being screened for responsiveness to the announcement prior to the review.

The R21 program evaluation yielded the following primary conclusions: (1) approximately one-third of new investigators choose to apply for the R21, even though there is a more generous payline for new investigator R01s; (2) the R21 success rate is comparable to—and in some cases exceeds—the R01 success rate, and these types of grants "compete" for the same payline; and (3) the majority of current awards are considered by their Program Directors to be somewhat or very well suited for the R21 program, but some awards have been made that are not particularly good matches for the program.

Dr. Nuckolls then discussed the perspectives of other ICs regarding the R21 program. The National Cancer Institute (NCI), National Institute of General Medical Sciences (NIGMS), National Center for Complementary and Alternative Medicine, National Center on Minority Health and Health Disparities, and Fogarty International Center (FIC) do not participate in the R21 parent announcement. The NCI has more than 30 different R21 PAs for specific research areas, but has found that, in some cases, these projects are not supporting the type of research for which the R21 is intended. The NIGMS has been using an RFA to support R21s; the Institute found that most of the applications were not fitting the category of high-risk and high-impact research, and so it developed the Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA**)** Program to address this need. The NIDDK participates in the NIH-wide R21 parent announcement and strongly encourages investigators to contact Program Directors prior to submission. Most of NIDDK's R21s are funded through select pay, and those applications that do not match the type of science the Institute is looking for are skipped. For the NIDDK, the R21 success rate is below that of their R01s. This approach appears to have reduced the number of non-responsive applications, but requires a great deal of up-front communication with investigators.

Dr. Nuckolls presented the Council with four options for the NIAMS R21 program:

- *Option 1: "No Change."* Continue to participate in the NIH-wide parent R21 announcement. Dr. Nuckolls commented that this option would have the following effects: (1) a continued impact on the R01 payline; (2) new investigators will continue to apply for this mechanism, even though an R01 may be better suited for them and their career; and (3) some projects will continue to be supported without matching the intent of the program.

- *Option 2: "The NIDDK Model."* Encourage more selective applications by announcing to the research community the NIAMS interest in R21s with high innovation/impact, making the payline more stringent, skipping applications through select pay, and encouraging applicant communication with and screening by Program Directors prior to submission.

Possible impacts include: (1) applicants choosing to apply for R21s more carefully, (2) Program Directors receiving more questions from potential applicants, (4) increased opportunities for Program Directors to recommend select pay, and (5) a more stringent payline may discourage applicants from choosing this activity code.

- *Option 3: "Revisit the Past."* Issue an RFA for high-innovation, high-impact R21s in arthritis and musculoskeletal and skin disease research. This approach would include strongly encouraging prior communication with Program Directors, screening applications for responsiveness prior to review, and possibly restricting applicants to investigators in specific career stages (e.g., experienced investigators). Impacts associated with this option include the requirement of set-aside funds, as well as IC review.

- *Option 4: "Drop the Parent Announcement."* Discontinue participation in the R21 parent announcement and reserve the R21 only for occasional PAs and RFAs for specific research areas. Possible impacts associated with this option include:
  - Funds from the R21 program could be used to support additional R01s (the effect on the payline would depend on the number of R01 applications and requested budgets).
  - Applicants may submit small R01s for exploratory studies (some may be innovative/high impact, most will have higher requested budgets)
  - It may increase the new investigator/ESI R01 applicant pool.
  - Reviewers may become accustomed to evaluating exploratory R01 applications.
  - Applicants may seek out TR01, EUREKA, or other mechanisms for appropriate projects.

Discussion

Council member Dr. Cliff Rosen, Director of Translational Research at the Maine Medical Center, asked about the percent of new investigators in the R21 program who go on to receive R01 awards. Dr. Nuckolls indicated that this analysis has not been carried out, in part because the NIAMS has not been participating in the NIH-wide parent R21 announcement for a long enough period of time. He noted that if the R21 mechanism was really intended for high risk research, one would not expect all of them to lead to R01 grants. Dr. Rosen also asked about the number of experienced investigators who were not funded for an R01 but were funded through the R21 program (e.g., as a "plan B"). Dr. Nuckolls explained that this analysis has not been carried out.

In response to another question, Dr. Nuckolls clarified that if a new investigator receives an R21 grant but then applies for an R01, he or she is still considered a new investigator. Dr. Kathleen Green, the Joseph L. Mayberry Professor in the Department of Pathology/Cancer Center at Northwestern University Medical School and a member of the Council, asked if the reason one-third of new investigators apply to the R21 program is due to a lack of understanding or communication regarding the program's intent. She noted that her understanding is that most new investigators who ask for guidance in this area generally choose to apply for an R01. Dr. Nuckolls commented that when he is asked by these applicants, he advises them to apply for new investigator R01s. Dr. Kathleen Green also noted that Option 2 presented by Dr. Nuckolls ("The NIDDK Model") would require an additional layer of communication and changing the existing paradigm of providing guidance. Dr. Katz added that communication between the Institute and

the scientific community represents a significant challenge, particularly in a case such as this in which the community has to use its mentoring skills to advise young investigators. Dr. Kathleen Green suggested that professional scientific societies could be a means to reaching out to young investigators and informing them of their options; Dr. Katz noted that this approach has been tried—some communities have embraced this more than others.

Dr. Serrate-Sztein commented that in her experience with advising applicants regarding particular funding mechanisms, the maturity of the project often is the deciding factor in opting whether to apply for an R21 or an R01. Dr. Crofford asked whether there was a history of success associated with the previous RFA tied to Option 3 ("Revisit the Past") as presented by Dr. Nuckolls. Dr. Nuckolls commented that the Institute has not yet analyzed the results of that RFA. The NIAMS felt that applications to the previous R21 RFA would be reviewed more effectively by standing study sections than by those within the Institute. Dr. Crofford expressed concern that standing study sections that are reviewing R01s expect preliminary data and that by not having a NIAMS-specific funding opportunity of R21-type efforts, these investigators may be at a competitive disadvantage.

Council member Dr. S. Wright Caughman, Professor in the Department of Dermatology at Emory University School of Medicine, commented that the R21 program appears to be a mechanism that was adopted and has had results that are different from its original intent. He suggested that the Institute consider whether the intent is something it wants to embrace, and as such will fund high-risk, innovative research as characterized by the R21 criteria. If that is the case, the Institute should be explicit in the R21 criteria and have a method in place to prescreen applications to ensure that they adhere to the criteria. Dr. Katz noted that the funding landscape has changed in the 5 or 6 years since the Institute started participating in the R21 program; Transformative R01s, New Innovator Awards, etc., have been added and have the capability of addressing the areas that the R21 program also was intended to address. Dr. Caughman suggested that if the Institute wants to fund this type of research but the mechanism is too cumbersome or expensive, NIAMS should consider utilizing a different mechanism that is more efficient in rewarding good science.

Dr. Kronenberg emphasized that having the Institute fund innovative research is very important. He suggested that the Council focus on Options 2 and 3 as presented by Dr. Nuckolls ("The NIDDK Model," and "Revisit the Past," respectively). He noted that funding innovative work for which there is not a great deal of preliminary data should be part of the NIAMS portfolio. Given where the payline is, Dr. Kronenberg noted that it will be hard to change the "clichéd" thinking of study sections that traditionally look to have experiments mostly complete before there is enough material to submit an R01 application. Dr. Kronenberg commented that the R21 is an important mechanism and that Options 2 and 3 presented by Dr. Nuckolls both have advantages and disadvantages. Having a great, innovative idea without enough preliminary data to successfully compete for an R01 may be more likely for a new investigator compared with an established investigator, because established investigators are able to use their other grants to obtain preliminary innovative data. New investigators do not have that opportunity. Dr. Kronenberg explained that the R21 should be reserved for truly innovative ideas for which there are not enough preliminary data to get an R01, and when used properly, is a wonderful opportunity for new investigators.

Dr. Katz commented that the NIDDK model (Option 2) would require NIAMS Program Directors to make decisions much earlier in the process on whether applications represent innovative science.

Dr. Diamond commented that having a mechanism such as the R21 is important, and that discussion to this point has, for the most part, eliminated Options 1 and 4 that were presented by Dr. Nuckolls. The issue becomes whether the NIAMS wants to review R21 applications internally or essentially prescreen and triage them before they go to a regular study section. She asked about the success rate of R21s at the NIDDK and commented that the NIDDK appears to be awarding only R21s that meet their criteria, following their internal screening process. Dr. Diamond suggested that if the NIDDK feels it got a lower percentage of these R21s through regular study sections, then the NIAMS should consider Option 3. If this is not the case, then Option 2 would reduce the NIAMS Program Director and staff workload. She echoed Dr. Kronenberg's earlier comment that the R21 should not be restricted to established investigators.

Dr. Sweeney indicated that the R21 is not supposed to be a mechanism for obtaining preliminary data. He commented that as a Department Chairman, he would never encourage a new faculty member to apply for an R21 to get preliminary data. There are university grants that allow faculty members to obtain preliminary data in advance of applying for an NIH grant. Young investigators who have an innovative idea that can be done in parallel with their main research should be allowed to apply for an R21. Dr. Sweeney added that even though it puts a burden on the Institute, it may be more advantageous to manage the R21s through an RFA, so that the Institute can fund applications that are more in line with its interests. Study sections appear to be giving R21s some leeway; there are a certain number of R21s—that do not necessarily meet the R21 criteria—that get ranked higher than they would if they were R01s in study section and would not normally be funded if they were submitted as R01s.
Dr. Rosen suggested that the NIAMS strongly consider selecting Option 2, which does put a burden on the Institute's Program Directors, but also identifies and removes those applications that are not program priorities. Dr. Crofford asked whether now is the right time to make a big change in the mechanism portfolio given the ongoing changes to the NIH-wide peer review system and how those changes may affect the overall Institute portfolio.

Dr. Nuckolls clarified that the study sections considering R21 applications that he has attended are looking for preliminary data—at least preliminary data addressing feasibility.

Dr. Jacobs noted that he is inclined to suggest that the NIAMS adopt Option 2. In response to Dr. Crofford's question regarding the timing of a change in how R21s are dealt with by the Institute, Dr. Diamond commented that established and new investigators likely would be accepting of the change, even in the face of a revised NIH-wide peer review system.

Dr. Katz explained that the NIAMS will conduct some internal discussions based on Council members' input. He acknowledged that Option 1 is not tenable for the Institute; neither is dropping use of the R21 altogether. Options 2 and 3 present potential models for the Institute with regard to the R21, which will remain open to established as well as new investigators. Dr.

Katz indicated that he will provide an update on NIAMS' decisions related to the R21 in his next Director's Report.

VI. HEALTH PARTNERSHIP INITIATIVE

Dr. Janet Austin explained that the NIAMS Community Health Center (CHC), which opened in 2001, is located within the Upper Cardozo Health Center in Washington, DC. The CHC provides area residents with access to specialty care and science-based health information. The Center also is a venue for community-based research on clinical aspects of rheumatic diseases, health education programs, and training for NIH staff. Patients at the CHC are enrolled in the Natural History Protocol for Rheumatic Diseases in Minorities an intramural research study designed to gather information on the severity and outcomes of rheumatic diseases. The CHC also serves as the platform for all of the NIAMS Health Partnership Program (HPP) activities. Dr. Austin explained that the HPP, established in 2000, is a collaborative effort between the NIAMS intramural research program, the NIAMS Office of Communications and Public Liaison, and the Washington, DC community. The HPP includes 68 partners representing various sectors of the African-American and Latino communities within the city. The Program evolved from the NIAMS belief in the importance of involving the community in the entire research process. Over the past 7 years, the Institute has demonstrated its commitment to serving minority communities through the HPP's five components (public health education, patient care, recruitment to research careers, community relations, and health disparities research).

Dr. Austin provided a brief timeline of the CHC and HPP, noting that at the request of community partners, a patient liaison program was established in 2001 to provide Cardozo clinic patients with easy access to services and care at the NIH Clinical Center. The CHC began enrolling at a rapid pace and started conducting a number of outreach efforts in the local community. Since January 2004, the CHC has been conducting quarterly patient satisfaction surveys and has consistently received high marks. Collaboration with other NIH ICs and the CHC also has evolved. Dr. Austin emphasized that significant effort was made to ensure the early involvement of the community in the research process. Any proposal for research studies to be conducted through the CHC is thoroughly vetted through the Center's (CHC not CC) community partners. In the past 7 years, there have been 352 outreach activities in the local area, 50 easy-to-read culturally-appropriate health information materials have been developed and distributed at the CHC and elsewhere, and there have been more than 500 patient visits to the NIH Clinical Center associated with the CHC and HPP.

CHC/HPP work has resulted in a number of articles about community engagement and research in peer-reviewed journals. A number of presentations on the CHC and HPP also have been given at national professional conferences. Dr. Austin noted that the CHC helps to facilitate HPP's goal of successful career development in a number of ways, including the NIAMS Summer Internship Program in Biomedical Research and the NIAMS Rheumatology Fellowship Program.

Dr. Mark Gourley, a rheumatologist and Director of Clinical Care and Training within the NIAMS Office of the Clinical Director, described CHC activities in more detail. One of the

Center's missions is the education of fellows. The CHC provides what Dr. Gourley termed "bread and butter" patients for rheumatology clinical care. During this training, there are 5 weekly half-day sessions, during which fellows typically see one new patient and three to five follow-up patients. All patients are referred, have primary care providers, and enroll in the minority disparities protocol. Care at the CHC is provided at no charge.

There are several barriers associated with seeing patients at the CHC. Dr. Gourley noted that about one-half of the patients seen there are Spanish speaking (the CHC features a bilingual staff and provides educational materials in Spanish). There also are challenges related to cultural differences and adherence (both to keeping appointments and to therapies). Dr. Gourley praised the CHC staff for working to achieve a "no-show" rate of only about 5 percent for appointments at the CHC.

Dr. Gourley described some of the research opportunities linked to the CHC. These include projects related to the ethics of research (e.g., exploring the ethics of clinical research in an urban community) and assessing primary care providers' knowledge (e.g., does educating the referring physician improve the quality of patient referrals?). Dr. Gourley noted that the health disparity protocol also allows screening of patients to enroll in other protocols at NIAMS and across the NIH.

Discussion

Dr. Katz emphasized the need for supporting, utilizing, and building trust with community partners. He added that other NIH ICs have expressed strong interest in becoming involved with the CHC. The Center has a very small space that was designed by Howard University architecture students. One particular challenge is that the community in the surrounding neighborhood has changed significantly in the 8 years since the CHC began operations. Although the CHC is very successful, there is some question as to whether it is still serving the same population that has, in general, moved away from the area. Ms. Evans also expressed some concern regarding the changing population around the CHC, and asked whether minority populations would still be able to access care there. Dr. Gourley agreed that the changing demographics in the area represent a challenge. Dr. Katz added that the individuals who run the CHC are committed to this community and the associated outreach programs.

Dr. Serrate-Sztein asked about the research protocols and patient population numbers, noting that some of these patient groups may be highly migratory, which can present challenges when defining a study protocol with specific numbers of patients. Dr. Gourley explained that all CHC patients are recruited into the minority disparities protocol, which often feeds into other protocols. For example, patients with certain conditions such as rheumatoid arthritis also typically are enrolled in the natural history protocol. He commented that in terms of demographics, the CHC sees patients from every continent and primarily sees patients that are Hispanic and African American. Dr. Katz noted that the CHC is located very close to a Metro station, which provides increased accessibility.

Dr. Klippel commented that this is a non-traditional role for the NIH and congratulated Drs. Gourley and Austin, as well as the entire CHC staff. He asked about the involvement of other

NIH ICs and community partners as well as the resources needed to fund this effort. Dr. Katz noted that the role of NIH in terms of patient care relates to research protocols, and that all patients at the CHC are enrolled into such protocols. The outreach component into the District of Columbia is somewhat non-traditional for the NIH, but the population served by the CHC represents a research base. In terms of other IC involvement, the NIH Clinical Center is an active participant, and the National Institute of Alcohol Abuse and Alcoholism, as well as the National Cancer Institute (NCI) are extremely interested in participating. The physical space constraints at the CHC (about 600 ft^2) make it difficult if not impossible to share the space. Dr. Gourley added that the NCI and the National Heart, Lung, and Blood Institute have used the CHC for outreach activities. In terms of resources, Dr. Katz explained that the CHC pays only $1 per year in rent. All other resources, including salaries, total approximately $500,000 per year. The Institute feels as though the CHC clearly represents a worthwhile investment and has improved its training program significantly.

Dr. Lee Green applauded the work of the CHC and HPP. He asked how patients are approached and asked to participate, as well as how community engagement is maintained. Dr. Austin noted that word of mouth through community partners was a critical component to drawing patients to the CHC. Other outreach efforts, such as exhibits and presentations, also helped bring patients in. Dr. Katz added that the CHC holds an annual meeting with community leaders, another important activity that raises awareness and draws in patients.

Council member Dr. Carmen Cheveres, a patient advocate, asked for a list of the CHC community partners, and noted that they deserve credit for participation in this important work. Dr. Austin indicated that her office would be willing to share that list of community partners. In response to a question from Dr. Caughman, Dr. Gourley explained that the CHC sees approximately 100-110 patients per month. Primary care physicians are asked to provide detailed referrals with laboratory and office notes. Generally, the wait time for appointments at the CHC is no longer than 2 months and is often earlier. Patient visits and appointments are triaged based on severity of illness.

VII. NIH GLOBAL HEALTH REPORT: OPPORTUNITIES IN ARTHRITIS, MUSCULOSKELETAL, AND SKIN DISEASES

The Fogerty International Center (FIC) Director Dr. Roger Glass, who also is the Associate Director for International Research at the NIH, participated in the meeting via videoconference from Kampala, Uganda. Dr. Glass noted that, although most think of research in Africa as being important for infectious diseases, one of the first tumors with a viral etiology (Burkitt's lymphoma) was identified in Africa. Furthermore, one of the first successful uses of chemotherapy occurred in Africa. Dr. Glass commented that there is a great deal to be gained by having young researchers visit a developing country and take advantage of training and other opportunities (he noted that Dr. Katz trained in Uganda in 1965). Dr. Glass provided a brief description of his experiences as a young investigator studying cholera in Bangladesh.

Dr. Glass emphasized the critical importance and value of early education in a young physician researcher's career to go out into the world, experience new diseases and new problems, and

develop solutions and research questions. He noted that FIC's mission is to: (1) address global health challenges through innovative and collaborative programs for research and training, and (2) support and advance the NIH mission through global partnerships. Dr. Glass explained that aging has changed the research portfolio for global health in the 21st century. Throughout the world, with the exception of sub-Saharan Africa, the chronic disease research agenda will become much more important with improving life expectancy rates. For example, life expectancy in China rose from 39 years in 1960 to 71 years in 2000—a prolongation of life of 8 years per decade for 4 decades. Skin and musculoskeletal diseases are some of the most cost-effective to treat in light of worldwide increased life expectancy. Dr. Glass presented a world map depicting global examples of emerging and re-emerging infectious diseases, adult and pediatric cancers, genetic diseases and disorders, and enduring environmental disasters. He commented that there is much that can be learned regarding chronic diseases in the 21st century, in which U.S. ingenuity coupled with opportunities in the developing world can break the frontiers of science.

Dr. Glass commented that the FIC portfolio includes an "alphabet soup" of federal programs that all involve collaborative research in global health, research training of foreign scientists in the United States and U.S. fellows training abroad, and interactions between institutions to develop research capacity. Dr. Glass explained that when he took the role of FIC Director, that the majority of the Center's grants in more than 100 countries addressed infectious disease and HIV. He hopes to expand the scope of science supported by the FIC to other areas of interest, including some that overlap with the scientific mission of the NIAMS.

Dr. Glass also explained that America's leaders in global health all have three things in common: (1) they are senior, white men; (2) they all studied infectious diseases in the 1970s, and (3) they all had early exposure to research in the developing world. To answer the question of where global health leaders for the 21st century (not just in terms of infectious diseases but also in terms of chronic diseases) will come from, Dr. Glass pointed to the International Clinical Research Scholars and Fellows Program as an example. As part of this program, predoctoral scholars, medical students in their third year, public health students, and postdoctoral students spend 1 year in research in a developing country. This program originally focused on infectious diseases but has been expanded to include chronic diseases. The FIC also has framework grants that bring university campuses together on the theme of global health research and training. Many of these grants are through U.S. universities partnering with universities and centers of excellence in the developing world. The FIC is facilitating the promotion of these long-term collaborations, building institutional capacity, and training future leaders. Dr. Glass also briefly described a number of projects in which the FIC is looking for collaborations, cooperation, and twinning to take research further and extend it both in the United States and overseas.

New advocates for global health (e.g., Bill Gates, Nelson Mandela, former U.S. Presidents Jimmy Carter and Bill Clinton) have helped renew global health. There also has been more money put into global health in the last 10 years than ever before (e.g., the President's Emergency program for AIDS Research and the President's Malaria Initiative). There is tremendous interest in global health on U.S. college and university campuses as students seek opportunities to work abroad, gain experience, and broaden their career interests.

Dr. Glass presented three concepts in FIC's strategic plan: (1) train the next generation of U.S. and foreign global health researchers; (2) build sustainable capacity for health science research, through institutional partnerships and research collaborations; and (3) advance implementation science as a tool for accelerating the application of research knowledge on a global scale. He noted that a recently released Institute of Medicine report has provided new recommendations for the U.S. commitment to global health. Seventeen different NIH ICs (including the NIAMS) provided input into the development of the report. In terms of opportunities for the NIAMS, Dr. Glass suggested that the following areas are ripe for investigation in the developing areas of the world:

- Skin diseases with HIV, infections with buruli ulcer, leprosy, leishmaniasis, etc.
- Genetic associations (e.g., keloids, fogo selvagem, albinism)
- Muscle diseases such as dystrophies
- Orthopaedics (e.g., trauma, osteoarthritis, club feet)
- Autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus
- Bioengineering (e.g., joints, stem cells)
- Telemedicine for treatment, research, and training.

Dr. Glass also presented his ideas on what the NIAMS can do in the area of global health, such as finding: (1) opportunities to study unusual diseases in settings where they are prevalent, (2) partnerships for clinical trials related to rare diseases, (3) populations with high rates of illness having clear genetic and environmental associations, and (4) centers of excellence in the developing world that could be good partners for research. In addition, the NIAMS could train and collaborate with researchers able to work comfortably in global health with key diseases in the NIAMS research portfolio. As an example, Dr. Glass described a regional dermatology training center in Moshi, Tanzania.

There are opportunities from FIC to support training through the following mechanisms: (1) the International Clinical Research Scholars and Fellows Program, (2) framework grants for global health at universities, (3) assistance with future clinical studies, (4) assistance in building relationships with centers of excellence, and (5) Fogarty International Research Collaboration Awards and Reentry Grants.

Dr. Nelson Sewankambo, Dean of the Medical Faculty at Makerre University, joined Dr. Glass by videoconference from Kampala. He thanked Dr. Glass and the NIAMS for the opportunity to participate in the Council meeting. He also agreed with Dr. Glass that focusing on global health is the right thing to do. Dr. Sewankambo expressed great enthusiasm that there is a new emphasis and advocacy for putting resources into non-communicable diseases in the developing world. He noted that Uganda and other African nations have witnessed a significant increase in chronic conditions such as diabetes mellitus, which was previously uncommon in Uganda.

Discussion

Dr. David Fox, President of the ACR, participated in the Council meeting remotely and thanked Dr. Glass for his presentation and comments, which were well timed given the growing interest in global health in the field of rheumatology. The ACR has been able to fund several pilot projects for 2009 in the developing world, with a focus on trying to build capacity for rheumatic disease care and training, with the goal of establishing training centers. It is hoped that these efforts, leveraged with other efforts and resources, will help to build a global rheumatology infrastructure and cadre of trained professionals. Dr. Glass noted that Dr. Sewankambo initially collaborated with the Johns Hopkins University and now works with many other U.S. universities. Dr. Fox noted that the ACR projects being funded involve collaborations that each span more than one region of the world.

Dr. Katz commented that the American Association of Orthopedic Surgeons (AAOS) has a long tradition of outreach to many of the countries in the developing world, particularly in sub-Saharan Africa. Dr. Jacobs elaborated, noting that the AAOS and other organizations in the musculoskeletal area have a number of programs that try to bring orthopaedic care into developing countries. Dr. Jacobs, President-Elect of the U.S. Bone and Joint Decade, noted that the organization is hosting a meeting in October 2009 to discuss these issues.

VIII. FIC INTERNATIONAL CLINICAL RESEARCH FELLOWS PROGRAM

Dr. Carl Baker of NIAMS' Division of Skin and Rheumatic Diseases explained that the Institute is considering becoming involved in FIC's International Clinical Research Fellows Program. The Program currently is supported by a number of NIH ICs (FIC, National Institute of Allergy and Infectious Diseases, NCI, National Eye Institute, NHLBI, NIDCR, National Institute of Nursing Research, and Office of the Director). The Program is managed by Vanderbilt University and the American Association of Medical Colleges through the FIC Research Scholars Support Center (which has been funded as an R24 since 2007).

The International Clinical Research Fellows Program provides a 1-year mentored research fellowship for residents, fellows, and postdoctoral health science trainees to conduct clinical research on diseases and conditions in developing countries. Both U.S. and non-U.S. citizens are eligible to apply. The application includes a brief collaborative research training proposal developed with the overseas site. Dr. Baker explained that if the NIAMS wants to participate in this program, it can add a statement of research interests to the next announcement for applications (which will be issued in August 2009). Fellows selected for the program must spend a minimum of 10 months at the overseas site. The cost to the Institute would be approximately $90,000 per fellow; Dr. Baker provided a breakdown of how those funds are allocated (e.g., $45,000 stipend, $15,000 in research training funds, $10,000 for foreign site infrastructure and administration, etc.). He asked the Council for their input on whether the Institute should get involved with this program.

Discussion

Dr. Katz commented that NIAMS' current investment in global health is minimal and mostly done through collaborative studies of special populations. Dr. Diamond, who sits on the ACR Board of Directors, suggested that this program would be a good way for the Institute to partner with organizations like the ACR and would help identify opportunities to conduct research in areas of interest to the NIAMS while helping to fulfill its obligation with regard to global health. Dr. Crofford discussed ACR taking over administration of the International League of Associations for Rheumatology (ILAR), noting that funds have been set aside for research and developing relationships with developing countries. There may be opportunities for NIH ICs, including NIAMS, to participate and leverage some of these ILAR funds.

Dr. Rosen asked about the program's funding mechanism and where investigators obtain the external funding that is necessary for the grant. Dr. Baker clarified that the NIAMS, if it participates, would do so through the FIC-run program by providing supplements, and would not require any infrastructure on the Institute's part. Dr. Katz noted that applications to date for the International Clinical Research Fellows Program have not yet included areas of interest to the NIAMS. If the Institute were to participate in the program, it would be able to include its mission areas in the program announcement and assess the response after a few years. He added that in the area of skin diseases, there is a tremendous amount of enthusiasm for working with patients in developing countries, particularly in sub-Saharan Africa.

Dr. Caughman asked if there were any data on the long-term outcomes from investment in this fellowship program. Dr. Katz explained that there are no numbers available yet, because the program is only 2 years old. Similar programs at NIAID and the Centers for Disease Control and Prevention have had encouraging results. Dr. Caughman suggested that the program should also include senior and mid-level researchers. Dr. Diamond suggested that this program be utilized in places where there is already an existing infrastructure. She also agreed with Dr. Caughman that the program should be open to anyone who wants to move their career in that direction. Dr. Aron Primack, Program Officer in FIC's Division of International Training and Research, explained that the postdoctoral applicants to the International Clinical Research Fellows Program are limited to those who are within 3 years of their doctoral degree. He added that one measure of success is an extensive list of peer reviewed journal articles written by these students. Although there is a significant level of success in terms of the science, it will take some time—possibly 10 years or so—before one will be able to tell if these investigators move on to become policy makers and senior researchers guiding their respective fields.

IX. LONG RANGE PLAN UPDATE

Anita Linde, Director of NIAMS' Office of Science Policy and Planning, provided a summary of the NIAMS long-range plan for FY2010-2014. She reminded Council members of the brief discussion on the long-range plan that occurred at the September Council meeting. Ms. Linde characterized the development of the NIAMS long-range plan as a collective effort driven by the Institute's extramural program scientific staff with a great deal of input from the extramural community (both the scientific community and members of constituent organizations). The long-range plan is not intended to replace the previous plan. It is intended to: (1) identify needs,

opportunities, and challenges; (2) provide a broad scientific outline to propel research progress; (3) continue to support the best investigator-initiated research ideas; and (4) communicate the Institute's perspective.

Ms. Linde presented the timeline for the plan's development, starting with a request for comments on the NIAMS Web site in September/October 2008, followed by roundtable discussions in November/December of that year. In the spring of 2009, a meeting with NIAMS Coalition representatives will occur, followed by the presentation of the draft plan to the Council for review in June. In July/August 2009, the plan will be posted on the NIAMS Web site for public comment; the final plan is expected to be presented to the Council in September and posted online. She explained that the public request for comments asked for the identification of the top three recent research advances, the most promising areas of science, the most pressing scientific and training needs, the greatest challenges to research progress and potential solutions, and gaps in training. A total of 38 comments were received from the Web-based request for comments; 25 were received from academic researchers, 9 from professional society/patient advocacy representatives, and 4 from patients/industry representatives/others.

Ms. Linde explained that there were three roundtable meetings held that encompassed the portfolio in the NIAMS Division of Musculoskeletal Diseases. These focused on musculoskeletal biology and diseases, bone biology and diseases, and muscle biology and diseases. For the NIAMS Division of Skin and Rheumatic Diseases, there were two roundtable discussions focused on arthritis and rheumatic diseases, and on skin biology and diseases.

Dr. McGowan noted that some cross-cutting themes emerged from all of the roundtable discussions. These included the need for training and maintaining a pipeline of investigators, promoting and supporting interdisciplinary and multidisciplinary training and collaborative opportunities, and overcoming challenges associated with integrating new technologies in genomics, proteomics, systems biology, and bioinformatics. Additional common, cross-cutting themes included the translation of basic research findings into therapeutics; optimizing approaches and managing and sharing data to facilitate progress in the area of genetics; the promise and challenges associated with stem/progenitor cells; biomarkers (imaging, as well as biochemical markers); and the design, use, and sharing of better animal models of disease.

Dr. McGowan briefly identified the themes discussed by the Musculoskeletal Biology and Diseases group:

- tissue engineering and regenerative medicine, including stem cell biology
- biomaterials (scaffolds, implants, and grafts)
- biomedical imaging (diagnosis, as well as biomarkers for treatment outcomes
- registries (implants and imaging), natural history cohorts (such as the Osteoarthritis Initiative) to inform new treatment strategies
- standardization of resources and technologies.

The Bone Biology and Diseases group covered the following areas:

- The interaction of bone with other systems and diseases (e.g., central nervous system, kidney, immune system)
- Wnt/b-catenin anabolic pathway
- Osteocyte biology
- Bone quality/bone strength assessment
- Therapeutics.

The Muscle Biology and Diseases group identified the following issues as being important as the Institute moves forward:

- Understanding muscle progenitor cell biology, expansion, and delivery for use in therapies
- Biological and molecular approaches to treat muscle diseases and disorders (e.g., myostatin inhibitors, gene therapy, antisense oligonucleotides, etc.)
- Novel treatment strategies to block or reverse atrophy, fatigue, and acquired myopathies
- Understanding the determinants of excitation-contraction coupling and force generation
- Muscle as a metabolic and endocrine organ and its interactions with other organ systems.

Dr. Serrate-Sztein provided the Council with a description of the most promising scientific areas, needs, opportunities, and challenges identified at the Skin Biology and Diseases roundtable. Detailed information is available in the NIAMS Web site. Some of the topics included:

- Stem cell biology and applications for regenerative medicine and wound healing
- Immunology and immune-related diseases of the skin, particularly cellular and molecular pathways of skin injury and targeting those pathways for therapeutics
- Genetics and genomics, and the need to develop cohorts and work collaboratively to characterize patients with particular diseases
- The study of comorbidities in the skin and skin manifestations of systemic disease
- The impact of burdensome regulatory requirements on skin studies

- Creative and innovative approaches to pursuing collaborations with investigators in other disciplines

- Opportunities for translational research on skin and skin-related diseases in the coming years.

Dr. Serrate-Sztein then presented the scientific needs, promising areas, and challenges covered by the Arthritis and Rheumatic Diseases roundtable. Discussions focused on:

- Immune and non-immune mechanisms of disease, and opportunities to take advantage of new and emerging technologies to understand immune response, immune dysregulation, and inflammatory processes at the systems level

- Genetics and genomics, and the need to expand cohorts through national and international efforts

- Whether or not new animal models of disease are needed

- Opportunities in biopsychosocial research

- The value of clinical trials and new methodologies.

Discussion

In response to a question from Dr. Diamond related to pain, Dr. Serrate-Sztein explained that during the Rheumatic Diseases roundtable, the discussions included biopsychosocial research and pain. Dr. Crofford added that pain is a tremendously large topic and that there was discussion of better clinical trials focused on assessing pain and better understanding pain biology. Dr. Kathleen Green asked about the number of people who responded to Chairs of the roundtable groups (the Chairs and roundtable participants solicited opinions from a variety of experts). Dr. Katz characterized the response as enormous; Dr. McGowan explained that there was a multiplier effect because of the large number of individuals who provided input. Dr. Kathleen Green also suggested that the draft long range plan be distributed to those who initially provided input. Dr. Katz indicated that this will be done and that many of the organizations with which the NIAMS works provided important comments as well.
Dr. Kronenberg noted that, with the exception of bone quality and therapeutics, the major discussions from the Bone Biology and Diseases roundtable could not have been anticipated in the previous long range plan for the Institute. He emphasized that in each of the fields represented by the roundtables, there are fast-moving topics that are identified and must be acted upon. The long-range plan should be flexible enough to account for this. Dr. Katz agreed and clarified that the long-range plan is not the Institute's strategic plan. The roundtables are meant to inform what efforts are needed.

X. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 946 applications in closed session requesting $342,160,383 and recommended 946 for $342,160,383.

XI. PORTFOLIO ANALYSIS

Dr. Marie Mancini, Health Science Administrator in the NIAMS Division of Skin and Rheumatic Diseases, led this discussion, which took place during closed session.

XII. ADJOURNMENT

The 67th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 3:00 p.m. Proceedings of the public portion of this meeting are recorded in this summary.

I hereby certify that, to the best of my knowledge, the foregoing summary and attachments are accurate and complete.

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