National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

June 2, 2009

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

MINUTES OF THE 68th MEETING

June 2, 2009
8:30 a.m. to 2:30 p.m.

I. CALL TO ORDER

The 68th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on June 2, 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
Dr. Leslie Crofford
Dr. Betty Diamond (by telephone)
Ms. Patricia McCabe Estrada
Ms. Karen Evans (by telephone)
Dr. B. Lee Green
Dr. Kathleen Green
Dr. Linda Griffith
Dr. Joshua Jacobs
Dr. John H. Klippel
Dr. Henry Kronenberg
Ms. Ann Kunkel
Dr. Clifford J. Rosen
Dr. H. Lee Sweeney
Dr. James Weinstein

Council members not present:

Dr. Kevin Campbell
Ms. Carmen Cheveres

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
Dr. Leslie Crofford
Ms. Wilma Peterman Cross
Ms. Teresa Do
Dr. Jonelle Drugan
Mr. Erik Edgerton
Ms. Sharon Fair
Ms. Barbara Footer
Dr. David Fuller
Ms. Gail Hamilton
Dr. Stephen Katz
Ms. Shahnaz Khan
Dr. Gayle Lester
Ms. Anita Linde
Ms. Mimi Lising
Ms. Leslie Littlejohn
Dr. Kan Ma
Ms. Emily Malone
Dr. Marie Mancini
Dr. Kathryn Marron
Dr. Joan McGowan
Ms. Leslie McIntire
Ms. Regina Mong
Ms. Melinda Nelson
Ms. Anna Nicholson
Dr. Glen Nuckolls
Dr. James Panagis
Dr. Charles Rafferty
Ms. Natalie Reyes
Ms. Trish Reynolds
Dr. Louise Rosenbaum

Ms. Karin Rudolph
Dr. Susana Serrate-Sztein
Dr. William Sharrock
Ms. Allisen Stewart
Ms. Robyn Strachan
Ms. Yen Thach
Ms. Jamie Thompson
Mr. Phil Tonkins
Mr. Hung Tseng
Ms. Marcia Vital
Dr. Fei Wang
Dr. Yan Wang
Dr. Chuck Washabaugh
Mr. Elijah Weisberg
Ms. Candice Williams
Ms. Sara Wilson
Dr. James Witter

Guests

Ms. Roberta Biegel, National Osteoporosis Foundation
Ms. Fettina Bryant, Office of the Director, NIH
Mr. Michael Bykowski, Consolidated Solutions and Innovations
Dr. Price Connor, National Institute for Occupational Safety and Health
Ms. Tanya Dougans, National Heart, Lung, and Blood Institute, NIH
Ms. Christy Gilmour, American Academy of Orthopaedic Surgeons
Mr. Aiken Hackett, American College of Rheumatology
Ms. Kim Holmes, IQ Solutions
Dr. Mahin Khatami, National Cancer Institute, NIH
Dr. Rebecca Minnillo, Society for Investigative Dermatology
Ms. Sheila Rittenburg, National Psoriasis Foundation
Dr. Sally Rockey, Office of the Director, NIH
Ms. Liz Schoonover, American Academy of Dermatology
Ms. Elaine Vining, National Psoriasis Foundation

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept with no changes the minutes of the 67th Council meeting, held on February 3, 2009.

III. FUTURE COUNCIL MEETING DATES

Future Council meetings are currently planned for the following dates:

September 16, 2009
February 2, 2010
June 15, 2010
September 28, 2010
February 1, 2011
June 14, 2011
September 27, 2011

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz welcomed Council members, NIAMS staff, and guests. He 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 American Recovery and Reinvestment Act (ARRA). Dr. Katz noted that the inclusion of the NIH in the nation's recovery efforts represents a tremendous vote of confidence from the President and Congress. It is essential that members of the research community heed the call to participate in the review process associated with ARRA applications.

Dr. Katz introduced Council member Dr. Linda Griffith, Director of the Biological Process Engineering Center at the Massachusetts Institute of Technology, who was attending her first Council meeting. He also congratulated Dr. Kathleen Green, who is the 2009-2010 President-Elect of the Society for Investigative Dermatology. Dr. Green is a member of the Council and the Joseph L. Mayberry Professor in the Department of Pathology/Cancer Center at Northwestern University Medical School.

Personnel Changes at the NIH/NIAMS

Dr. Katz noted that a new NIH Director had not been named as of this Council meeting.

At the NIAMS level, the Institute is still searching for a new Director for its Division of Extramural Research Activities (DERA). It is hoped that this position will be filled this summer. In the interim, Ms. Melinda Nelson, Chief of the NIAMS Grants Management Branch, is serving as the DERA Acting Director. Dr. Charles Rafferty has been selected as the new Chief of the NIAMS Scientific Review Branch. Dr. Katz acknowledged and thanked Dr. Helen Lin for serving as the Acting Scientific Review Branch Chief. Dr. Su-Yau Mao has joined the NIAMS Division of Skin and Rheumatic Diseases as the Director of the Arthritis Biology Program. Within the NIAMS Office of the Director, Dr. Branden Brough has joined the Institute's Office of Science Policy and Planning (OSPP) as a Program Analyst. Within the Intramural Program, Dr. Timothy Bhattacharyya has joined the Clinical and Investigative Orthopaedics Section. Dr. Rocky Tuan, Senior Investigator within the NIAMS Intramural Cartilage Biology and Orthopaedics Branch, is leaving the NIH to serve as the Director of the Center for Cellular and

Molecular Engineering within the Orthopaedic Surgery Department at the University of Pittsburgh School of Medicine.

Dr. Katz recognized a number of NIAMS staff who have received awards for their distinguished work:

- Dr. John J. O'Shea, Scientific Director of the NIAMS Intramural Research Program, received the 2009 Irish Society for Immunology Public Lecture Award, sponsored by the Royal Dublin Society and *The Irish Times*.

- The NIAMS Office of Communications and Public Liaison (OCPL) received two Blue Pencil Awards of Excellence from the National Association of Government Communicators. The Institute received awards for its electronic hall display and the NIAMS Health Zones materials for NIH's Take Your Child to Work Day. Dr. Katz invited Council members to visit the NIAMS electronic hall display, which has new videos on the: (1) NIH-National Aeronautics and Space Administration (NASA) Space-Based Human Health Research Initiative, (2) Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) Trial, and (3) activities of the NIAMS Coalition.

- NIAMS staff from the OCLP and OSPP were recognized at the 2009 NIH Plain Language Awards Ceremony later that day. Dr. Janet Austin, Susan Bettendorf, Mimi Lising, Melanie Martinez, Leslie McIntire, Trish Reynolds, Karin Rudolph, and Julie Townshend were recognized for their work on two bone health publications. Ms. Anita Linde and Drs. Jonelle Drugan and Louise Rosenbaum were recognized for Congressional materials that they prepared.

- Ms. Nelson received a Special Recognition Award from NIH's Vision Steering Committee in recognition of her time, insights, and contributions to ensure the high standards of NIH's Grants Professional Certification Program.

Update on Budget and Congressional Activities

With regard to Fiscal Year 2009 (FY 2009), on March 11, 2009, President Obama signed the Omnibus Appropriations Act into law. The Act provides $30.3 billion for the NIH, an increase of approximately 3 percent over the FY 2008 enacted level, including the $150 million in supplemental funds. The FY 2009 funding level for the NIAMS under the bill is $524.9 million, which is approximately 2.7 percent over the FY 2008 level. In accordance with NIH policy, non-competing awards will be issued at the most recently committed levels. Based on a case-by-case review of grant applications, reductions from direct costs recommended for new and competing awards will be approximately 10 percent; Dr. Katz also noted that the Institute is pleased to be able to maintain the payline for competing R01 and R21 applications this year at the percentile of 15.0, and at 18.0 for R01 applications from new investigators. This percentile has remained fairly constant during the last 4-5 years, which has been an important goal. Dr. Katz reminded Council members that additional information on all established paylines and funding policies for the Institute can be found on the NIAMS Web site.

For FY 2010, the President's Budget request was released on May 7, 2009. The request provides $30.8 billion for the NIH, an increase of approximately 1.5 percent over the FY 2009 appropriation, not including the $10.4 billion from ARRA. The proposed funding level for the NIAMS under the current request is $530.8 million, which is approximately 1.1 percent over FY 2009, excluding the ARRA funds. Support for new and early-stage investigators will remain an important goal, and the NIAMS will make every effort to maintain its success rate at at least 20 percent.

Dr. Katz reported that the President's Budget for FY 2010 includes an 8-year commitment to double cancer research funding from $5.5 billion in FY 2010 to $11 billion by FY 2017. He noted the important distinction between "cancer research funding" and "the National Cancer Institute (NCI) budget." This opportunity affects not just the NCI, but also the 23 other Institutes and Centers (ICs), the NIH Director's Office, and the Common Fund. Dr. Katz is working with NCI Director Dr. John Niederhuber as Co-Chair of an NIH-wide effort to identify and describe cancer research activities that the NIH will undertake in the next 8 years. A Strategic Plan to double the NIH Cancer Research Budget is being prepared for submission to the Office of Management and Budget (OMB) to identify these opportunities.

Dr. Katz explained that the delayed release of the FY 2010 President's Budget led to changes from the usual Congressional Appropriations hearings schedule. The House Appropriations hearing on March 26 focused on ARRA, not the FY 2010 President's Budget, which at that time had not been released. That hearing also examined the current status of the National Children's Study. Acting NIH Director Dr. Raynard Kington testified on the FY 2010 budget request before the Senate Appropriations Subcommittee on May 21; he was accompanied by several IC Directors, including Dr. Katz.

On April 28, Kansas Governor Kathleen Sebelius was confirmed by the Senate as the new Secretary of the Department of Health and Human Services (DHHS). On May 7, Bill Corr was confirmed as DHHS Deputy Secretary.

During the 110th Congress, members introduced numerous bills on topics of great interest to the NIAMS. These include:

- Prevention, Awareness, and Research of Autoimmune Diseases Act of 2009
- Arthritis Prevention, Control, and Cure Act of 2009
- Access to America's Orthopaedic Services Act of 2009
- Cures Acceleration Network and National Institutes of Health Reauthorization Act of 2009
- National Pain Care Policy Act
- Psoriasis and Psoriatic Arthritis Research, Cure, and Care Act of 2009.

Dr. Katz directed Council members to the ShortTakes newsletter, which provides additional information on these and other Congressional items of interest, along with related Web links.

Highlights of Selected Recent Scientific Advances

Extramural Research

- A new analysis from the Osteoporotic Fractures in Men (Mr. OS) Study showed that bone loss at the hip in older men is modest on average. But it uncovered two factors that should help to identify those men who need direct targeted interventions: (1) men whose bone loss accelerates with age; and (2) men who have the lowest bone mineral density at baseline, as they are at greatest risk of increased bone loss (*J Bone Miner Res.* 2009 May 6 [Epub ahead of print]).

- Dr. Eric Orwoll and colleagues conducted a separate analysis from the Mr. OS Study. In a multicenter effort, they showed that combining finite element analysis modeling from QCT data with DXA improves fracture risk assessment in older men. A non-invasive strategy with an improved ability to predict fracture risk in both men and women will enable physicians and patients to make informed decisions about the need for treatment, and to continue to evaluate whether the selected treatment regimen is beneficial (*J Bone Miner Res.* 2009 Mar;24(3):475-83).

- A 4-year follow up study has been published in the October issue of *Journal of Bone and Joint Surgery* from Council member Dr. James Weinstein and colleagues. The researchers found that the results of surgical versus non surgical treatment of lumbar degenerative spondylolisthesis holds up well and that surgery is the preferred mode, but there is a patient choice aspect of the study, which demonstrates that when patients do have the option, most of them that selected surgery performed better. This work emphasizes the importance of informed choice for these types of interventions (*J Bone Joint Surg Am.* 2009 Jun:91(6):1295-304).

- Dr. Fred Kaplan and colleagues recently published mouse-model studies on the cellular pathways in the rare bone disease fibrodysplasia ossifican progressiva (FOP), which is characterized by heterotopic ossification—an abnormal development of bone in soft musculoskeletal tissues, such as connective tissues and muscles. The researchers found that although vascular smooth muscle precursors and skeletal muscle precursors had only minor roles in abnormal bone formation, the vascular endothelial precursor cells contributed significantly (*Bone Joint Surg Am.* 2009 Mar 1;91(3):652-63).

- An international team of researchers led by Dr. Johnny Huard's laboratory identified and isolated perivascular cells from several adult and fetal tissues and demonstrated that the cells were multipotent—they generated myogenic, adipogenic, chondrogenic, and osteogenic cell lineages *in vitro*, regardless of their tissue of origin. Furthermore, the pericytes had therapeutic potential, as they could produce muscle cells when injected into diseased or damaged muscle in mice. Although much more work is needed before these findings can be applied to clinical practice, the identification of multipotent cells in readily available tissues

(e.g., adult fat) has promising applications for tissue engineering and cell-based therapies (*Cell Stem Cell*. 2008 Sep 11;3(3):301-13).

- Dr. Jerry Mendell and colleagues conducted a 3-patient Phase I safety trial designed to test the delivery and expression of the alpha-sarcoglycan gene and to assess immune responses against the alpha-sarcoglycan protein in patients with the 2D form of limb-girdle muscular dystrophy. Each patient had the gene therapy construct injected into a small muscle in one foot; a saline control was injected in the same muscle in the other foot. The results demonstrated the safety of the procedure; expression of the transferred gene was achieved for at least 12 weeks after injection. There was no detectable immune response to the alpha-sarcoglycan protein. However, antibodies to virus proteins were detected in the blood, and there was some evidence of inflammation. Evidence from patient biopsies suggested that alpha-sarcoglycan protein was forming normal complexes with other proteins in the muscle cell membrane. A biopsy from one of the three patients showed that the average cross-sectional diameter of muscle cells was larger in the treated muscle than in the control. This unexpected finding suggests that the treatment may increase muscle regeneration, but warrants further investigation in studies that specifically are designed to evaluate whether the therapy restores muscle function (*Annals of Neurology*. Accepted Article Online: Apr 16 2009).

- Dr. Elaine Fuchs and colleagues have identified and characterized a critical enzyme, Ezh2, which is involved in stage-specific regulation of cell proliferation and differentiation in the developing epidermis. Ezh2 facilitates chemical modification of proteins that control gene expression, and these chemical changes affect pathways involved in the sequential steps of skin layer formation. When Ezh2 is eliminated in a mouse model, aspects of normal epidermal development are impaired. Because this activity is inherited, but it is not contained in the cell's DNA, it is called "epigenetic" (*Cell*, 2009 Mar 20;136(6):1122-35.)

- Dr. Miikka Vikkula and his collaborators have been studying venous malformations in large families over several years, and have found an inherited mutation. Most recently, they identified non-heritable mutations, or somatic mutations, that occur during childhood development or adulthood. In combination with the heritable mutations, these somatic mutations may be partial causes of sporadic venous malformations. The current treatment for these lesions includes lasers to burn the malformed vessels off of the skin surface. This intervention tends to be painful, inconvenient, and is less effective for deeper and internal lesions. These findings identify factors involved in the generation of venous malformations that may be targets for biologic or pharmacological treatments (*Nature Genetics.* 2009 Jan 41(1):118-24).

- One of the genes associated with lupus risk, IRAK-1, is located on the human X chromosome. The IRAK-1 protein has a critical role in regulation of the immune response—it can initiate a cascade of molecular signaling events, leading to expression of genes associated with inflammation. An international collaborative effort, led by Dr. Chandra Mohan, recently found five IRAK1 gene variants. Results of their work provide compelling evidence that support IRAK1 as a disease gene in lupus. In addition, its location on the

human X chromosome is a possible explanation for female predominance of the disease (*Proc Natl Acad Sci U S A.* 2009 Apr 14; 106(15): 6256-61).

Intramural Research

- Drs. John O'Shea and Juan Rivera have recently discovered that the protein Lyn kinase, expressed in immune cells called basophils, helps control the way T helper cells differentiate in mice. T cells may differentiate into Th1 or Th2 cells, depending on the foreign agent, or antigen, to which the immune system is reacting. However, if the ratio of Th1 to Th2 cells is skewed too much toward one type or the other, then the body's immune response can go awry. This ability to govern T helper cell differentiation makes basophils and their cell-signaling pathways possible targets for future therapeutic strategies in lupus and other immune-mediated diseases (*Immunity*. 2009;30(4):533-543).

- Scientists from the NIAMS Intramural Research Program and other institutions have discovered a new autoinflammatory syndrome—a rare genetic condition that affects children around the time of birth. The team, led by Drs. Dan Kastner and Raphaela Goldbach-Mansky have termed the new autoinflammatory syndrome "deficiency of the interleukin-1 receptor antagonist" (DIRA). Children with the disorder display a constellation of serious and potentially fatal symptoms. Most of the children begin to have symptoms from birth to 2 weeks of age. All the children in the study had inherited mutations in IL1RN, a gene that encodes a protein known as interleukin-1 receptor antagonist (IL-1Ra). Without IL-1Ra, the children's bodies cannot control systemic inflammation that can be caused by interleukin-1.

  The scientists identified nine patients with DIRA from six families in the Canadian province of Newfoundland, the Netherlands, Lebanon, and Puerto Rico. Although the patients were resistant to other medications such as steroids, most responded successfully and immediately to anakinra (a drug that is normally used for rheumatoid arthritis and is a synthetic form of human IL-1Ra). Although the mutation that causes DIRA is rare, as many as 2.5 percent of the population of northwest Puerto Rico are carriers. Because the mutation was found in three independent Dutch families, newborn screening for DIRA in this population, as well as that of northwest Puerto Rico, may be warranted.

NIH/NIAMS Activities and Plans for the Future

The NIH is seeking comments from the public on possible changes to federal regulations regarding financial conflicts of interest in federally funded research.

On March 9, 2009, President Obama authorized the DHHS Secretary, through the NIH Director, to support and conduct responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted by law. The President also charged the NIH Director with reviewing existing guidelines on human stem cell research, and issuing new guidance within 120 days. More information is available online at stemcells.nih.gov.

Another NIH policy change comes from the 2009 Omnibus Appropriations Act, which made the NIH's Public Access Policy permanent to ensure that the public can read published results of NIH-funded research.

With ARRA funding, Congress allocated $1.1 billion for comparative effectiveness research through the NIH, the Agency for Healthcare Research and Quality (AHRQ), and the DHHS Office of the Secretary. ARRA also established the Federal Coordinating Council for Comparative Effectiveness Research to coordinate the ARRA-funded comparative effectiveness research portfolio.

Under the NIH Reform Act of 2006, Congress established the NIH Scientific Management Review Board to evaluate how the structure and organization of the NIH can be improved to fulfill its mission. Dr. Katz (and many other IC Directors) serves on this Board, which had its first meeting in April. Former NIH Directors Dr. Harold Varmus and Dr. Elias Zerhouni both addressed the Board. Key discussion topics included whether the NIH should consider merging the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, and how best to position the NIH intramural research program and Clinical Center for future productivity and success.

Dr. Katz briefly discussed the Patient-Reported Outcomes Measurement Information System (PROMIS), which is part of NIH Roadmap efforts to re-engineer the clinical research enterprise. The NIAMS has been overseeing PROMIS since it was launched as a 5-year program in 2004, and the noteworthy efforts of several NIAMS staff (including Drs. Susana Serrate-Sztein, Jim Witter, and Louise Rosenbaum and Ms. Barbara Footer) prompted the NIH Roadmap to commit another 4 years of funding to the initiative, through FY 2012. Applications are in for the four RFAs that were put out for the next phase of this effort; additional information on PROMIS will be presented at the September Council meeting.

Dr. Katz noted that the Institute has an active program in information dissemination and health outreach programs, led by Dr. Janet Austin. On the day following this Council meeting, the NIAMS will host its first planning meeting of the Multicultural Outreach Initiative *Ad Hoc* Group of the NIAMS Advisory Council. The following Council members have agreed to serve on this group: Mr. George Beach, Ms. Carmen Cheveres, Dr. Lee Green, and Ms. Ann Kunkel.

The NIAMS continues to lead the Trans-NIH American Indian and Alaska Native (AI/AN) Health Communications and Information Workgroup, composed of representatives from 16 NIH ICs. The Workgroup's main purpose is to coordinate efforts in developing and disseminating health information to AI/AN communities.

Dr. Katz concluded his report by describing some of the Institute's ongoing information-dissemination efforts. Council members were provided with compact discs containing audio recordings that are part of NIAMS' efforts to extend the reach of the Institute's health information about bones, joints, muscles, and skin diseases. The CDs contain MP3 files that have been posted on the NIAMS Web site for users to download to their computers or their hand-held MP3 players. Council members also were provided with a copy of the January-February edition of *The NIH Catalyst*, which contains an interview with Dr. Dan Kastner,

Clinical Director of the NIAMS Intramural Research Program and NIH Deputy Director for Intramural Clinical Research. Additionally, Council members were given an excerpt from the Spring 2009 issue of *MedlinePlus Magazine*, which highlights several NIAMS research initiatives related to osteoarthritis, and includes a profile of Dr. Rocky Tuan. At the end of his Director's Report, Dr. Katz presented a 3-minute television feature focusing on Dr. Goldbach-Manksy and her work on the cryopyrin-associated periodic syndrome NOMID (neonatal-onset multisystem inflammatory disease), which was featured in a recent segment for the series *Healthy Body, Healthy Mind*, which airs nationally on PBS.

Discussion

Council member Dr. James Weinstein, Professor and Chair of the Department of Orthopaedics at Dartmouth-Hitchcock Medical Center, asked about the increase in funds to be allocated for cancer research across the NIH ICs, noting that bone symptoms are common in metastatic disease. He asked if some of these funds could be used to examine new treatment modalities for bone-related cancers. Dr. Katz indicated that this is the case, and noted that the NIH leadership is developing a document to illustrate the possibilities presented by a doubling of the cancer budget over the next 8 years (approximately 17 percent of cancer research at the NIH is carried out by ICs other than the NCI). Dr. Katz further explained that the President's commitment to the cancer effort is a reflection of his priorities; it is unclear at present how this doubling in funds will occur, however. The NIAMS intends to expand and promote its cancer-related efforts, while being careful not to move into areas traditionally funded by the NCI.

Council member Dr. Jack Klippel, President and CEO of the Arthritis Foundation, noted that the interview with Dr. Kastner in the *NIH Catalyst* is outstanding and suggested that it would be valuable for Council members to hear more about the needs, opportunities, and advances associated with the Institute's Intramural Research Program. Dr. Katz noted that Dr. Kastner made a presentation at a recent Council meeting on the Center for Human Immunology; Dr. Kastner will be asked to provide additional information on the Intramural Research Program at a future Council meeting.

V. IMPLEMENTATION OF RECOVERY ACT AT NIH

Dr. Sally Rockey, NIH Acting Deputy Director for Extramural Research, noted that the NIH is grateful to President Obama and Congress for the opportunity to play its part in improving the nation's health and economy. In terms of impact, the ARRA funding is expected to stimulate the economy, create and preserve jobs, and advance biomedical research. ARRA appropriated $10 billion directly to the NIH, broken down as follows: $0.3 billion for extramural scientific equipment; $0.5 billion for intramural repair, improvements, and construction; $1 billion for extramural repair, improvements, and construction; and $8.2 billion for extramural scientific research. ARRA also appropriated $400 million to the NIH for comparative effectiveness research via the AHRQ.

Dr. Rockey explained the scientific research approach to utilizing these ARRA funds, which involves stimulating and accelerating biomedical research with existing mechanisms. Additional

meritorious R01s, R21s and R03s, R24s, and R43s that have been peer reviewed and approved by IC Councils are being funded (many ICs have used up to 60 percent of their ARRA funds in this way). Up to $1 billion is being used to accelerate ongoing research through administrative supplements to existing grants. ARRA funds are also being used to expand science with new programs (e.g., revisions to extant programs, new ARRA NIH-wide programs, and new ARRA IC-specific programs).

Dr. Rockey described the following new ARRA NIH-wide programs:

- *Challenge Grants*. The Challenge Grants (at least $200 million total from the NIH Director and individual ICs) provide priority avenues of research for ICs. These grants allow for up to $500,000 in total costs per year for up to 2 years. There were 15 major areas defined as high priority topics (e.g., biomarker discovery and validation, comparative effectiveness research, genomics, etc.). More than 20,000 applications were received; it is anticipated that between 200 and 700 Challenge Grant awards will be made by September 30, 2009.

- *Grand Opportunity Grants*. The Grand Opportunity (GO) Grants are designed for well-defined studies of high impact and large scale. They have no limit on the amount of money that can be applied for. More than 1,000 letters of intent and more than 1,000 applications have been received to date.

- *Signature Initiatives.* These awards support exceptionally creative projects to address major challenges in biomedical research. Examples include nanotechnology, genome-wide association studies, Alzheimer's disease, oral fluids as biomarkers, large-scale sequencing, and community-based research.

- *Recruiting New Faculty to Conduct Research*. Dr. Rockey explained that the Core Centers for Enhancing Research Capacity in U.S. Academic Institutions can provide start-up packages for recruitments that may have stalled for economic reasons. These Centers promote the hiring of newly trained scientists and assist them in starting up pilot research projects. The recruitment of bioethicists is among one of the main priorities.

- *Providing Summer Jobs for High School /College Students and Teachers to Work in Science Laboratories.* This program is intended to expose high school and college students to biomedical research, encourage students to pursue research careers, and provide summer internships at NIH-funded laboratories for science teachers. More than 1,000 of these awards will be given (including at least one in every state), with the anticipated creation of approximately 4,000 jobs for students over the next 2 summers.

- *IC-Specific RFA: $60 Million in Grants for Strategic Autism Research.* One disease-oriented RFA associated with ARRA involves a $60 million grant program on research to address the heterogeneity in autism spectrum disorders.

- *AREA (R15) Grants.* The Academic Research Enhancement Awards (AREA) are granted to applicants from domestic institutions/organizations and provides $300,000 in direct costs for

up to 3 years. This program extends NIH support across the United States and allows for the inclusion of institutions that typically do not participate in NIH programs.

Dr. Rockey provided an update on the $800 million in ARRA funds allocated to the NIH Office of the Director (OD): $200 million is being set aside for Challenge Grants, $30 million is earmarked for OD-IC Community Signature projects, $30 million will go to IC-OD Signature projects, $21 million is set aside for summer training projects, $10 million for faculty recruitment, and $30 million for AREA Grants. There is a total of $509 million in funding that is yet to be determined. The NIH Common Fund also received an ARRA allocation of $120 million to stimulate and accelerate biomedical research with existing mechanisms.

In terms of expected reporting requirements, all ARRA grants must have separate accounts and draw downs are from each account. Organizations that receive NIH grants with ARRA funding will be required to report directly to a federal reporting site on the number of jobs, expenditures, and project status. The NIH will also have to provide in-depth reports on these funds and how they are used. Dr. Rockey noted that there is a great deal of information available online at www.nih.gov/recovery and encouraged Council members to visit the site.

Discussion

Dr. Katz opened the discussion session by noting that at the NIAMS, Deputy Director Dr. Robert Carter has taken charge of ARRA issues as they relate to the Institute; Drs. Joan McGowan and Susana Serrate-Sztein have provided invaluable assistance as well. Dr. Katz explained that the tremendous application response rate demonstrates the untapped capacity in this country for conducting scientific research. He reminded Council members that these ARRA funds are for U.S.-based research projects. Dr. Katz reported that the NIAMS received approximately 140 of the more than 1,000 letters of intent for GO Grants.

Dr. Weinstein noted that the approximately 3 percent success rate associated with the Challenge Grants may lead to a great deal of disappointment on the part individuals who worked hard in a short period of time to prepare their applications. He also asked about how the comparative effectiveness funds would be allocated. Dr. Rockey explained that the decisions regarding comparative effectiveness funds are still being made; the definition of the term "comparative effectiveness review" that will finally be settled upon by the federal coordinating committee is somewhat broader than the definition that appears in the RFA. Dr. Katz agreed to share this committee's draft definition with the Council that afternoon. He also clarified that the comparative effectiveness review grants will come from Challenge Grants reviewed by the Center for Scientific Review or the GO Grants, which will be reviewed by individual ICs.

Council member Dr. Joshua Jacobs, an orthopaedic surgeon at Rush University Medical Center, asked Dr. Katz about the allocation of ARRA funds within the NIAMS, particularly with regard to allocating funds between peer reviewed and non-peer reviewed applications. Dr. Katz indicated that the Institute will participate fully in all ARRA-related activities. The NIAMS plans to extend its payline at the 20th percentile for 2 years. It is unknown exactly what will come in for the Challenge Grants and what will come in for the GO Grants.

Philosophically, the Institute is looking to utilize ARRA funds in ways that offer extraordinary opportunities for research. At first, more money was put into the GO Grants as opposed to the Challenge Grants. Initially, it was not known that there would be such a tremendous response to the Challenge Grant and Go Grant solicitations; consideration was given to extending the payline beyond the 20 percent payline for awardees to have R01s for 2 years rather than 4 years. Now, most of the Institute's investment will involve the Challenge and GO Grants.

In response to a question regarding administrative supplements, Dr. Katz explained that at the NIAMS, Program Directors will review these projects and recommend meritorious ones in priority order to Division Directors, who will then make recommendations to Drs. Katz and Carter, who will in turn make the ultimate decisions based primarily on Program Director input. Dr. Kathleen Green asked about the 1,500 competing revisions that have been submitted and what percentage of parent grants have corresponding competing revisions and whether they are distributed evenly across NIH ICs. Dr. Rockey replied that she did not have specific numbers, but her sense is that many of the competing revisions are supplements for R01s. Although distributed across ICs, there are some Institutes that received a higher percentage of these competing revisions.

Council member Dr. Henry Kronenberg of the Department of Medicine at Harvard Medical School/Massachusetts General Hospital applauded the distribution to GO Grants, Challenge Grants, and administrative supplements. He noted that routinely all of the federally approved grants are cut by a certain percentage, so in some ways portions of the administrative supplements could be viewed as paying for projects that have already been reviewed but not paid for. Dr. Katz emphasized that the OMB has made it clear that ARRA funds are not to be used to replenish these types of cuts.

Council member Dr. Leslie Crofford, Director of the Center for the Advancement of Women's Health and Chief of Rheumatology at the University of Kentucky, agreed with Dr. Katz's earlier comment that the overwhelming response to these initiatives underscores the untapped potential in biomedical research across institutions in the United States. She asked about NIH's strategy or plans to translate this response to the federal government and use this as a way to let Congress know about these opportunities in an effort to leverage future NIH funding. Dr. Katz commented that this will be a challenge; there is the experience of the NIH budget doubling to draw upon, and the Institute will take advantage of every opportunity it can to underscore that there is a tremendous untapped capacity available. Dr. Rockey added that NIH's advocates on Capitol Hill have heard and appreciate this message.

Dr. Katz explained that there are administrative costs associated with these grants because of the separate reporting requirements associated with ARRA funds.

Dr. S. Wright Caughman, Professor in the Department of Dermatology at Emory University School of Medicine and a member of the Council, commented that this is a time when endowments and funding at the institutional level are being cut back. However, there is a tremendous push for all of the ARRA opportunities but diminished resources at the local level coupled with increased administrative reporting burdens and responsibilities.

Dr. Jacobs asked about the Council's role in the review of ARRA-related grants. Dr. Katz explained that the Challenge Grants will go to a 3-person editorial board, which will provide mail reviews and scores for individual components of the grants. Each application will undergo this scientific review, and a certain percentage will be given a final score. ICs then will be asked to provide a précis and priority list for their applications. Those applications will be submitted to a 5-person review board (consisting of IC Directors including Dr. Katz), which will make recommendations to the NIH Director (or NIH Acting Director) for funding certain applications through the Director's Fund. Those applications not funded through the Director's Fund will be adjudicated at the IC level. The Institutes' Councils will be asked to participate in this secondary review of applications. With regard to the GO applications, they are being reviewed within the NIAMS. Two review groups are being formed; following reviews, Program and Division Directors will make recommendations to Institute leadership.

Dr. Klippel noted that some measure of accountability will be needed when the government reviews progress made based on the ARRA investment. In many ways, Congress was asking for this when the NIH budget was doubled. There is an opportunity, through NIH's allocated ARRA funds, to make significant progress, report back to Congress, and convince lawmakers to support NIH even more in the future. Dr. Rockey agreed, noting that her office is working diligently on this issue. There are well-established methods in place for reporting on outputs; reporting on outcomes is more challenging, and is a primary focus of the entire federal government. Dr. Carter noted that another challenge is presented by the fact that ARRA requirements do not allow for a 3-5 year wait period for scientific studies to be conducted, analyzed, submitted for publication, and eventually, published. Reporting scientific advances that have not been published is an interesting question; one approach may be to use abstracts. Dr. Klippel suggested that the patient communities be approached to serve as partners with and champions of the NIH. Dr. Katz agreed, noting that in the last 15 years, the patient community and the public have impacted tremendously on why the Congress is now enthusiastic about the NIH. He added that the dissemination discussed by Dr. Klippel is extremely important.

VI. NIAMS TRAINING GRANTS

Dr. Carter reminded Council members of NIAMS' ongoing effort to refocus its training programs across all of the different mechanisms (e.g., K, F, T awards). This process started when the NIAMS convened a committee of extramural faculty and hired a contractor to help NIAMS understand what was being accomplished with the training portfolio and who it was serving. The committee focused on the T32, F32, K01, and K08 awards, and tracked awardees over a decade. Dr. Carter noted that awardees of F and K series awards showed remarkable success. For each, at least 80 percent of awardees went on to receive NIH funding beyond the training program.

Dr. Carter focused on one of the committee's recommendations: "Reward integrated and interdepartmental approaches, foster motivation, and support interdisciplinary mentorship." The committee developed a document, which is available online and includes its quantitative analysis. A roundtable discussion was held in April of this year to consider the committee's recommendations and what to do with the balance of the different types of mechanisms to

support trainees. Dr. Carter summarized that there was little agreement on how best to move forward. One idea that did have general support was that the criteria for review of the T32 awards needed to be clarified, because study sections have difficulty understanding what is called for and instruction from the NIH on the T32s is fairly complex.

Dr. Carter focused on the T32 program, noting that the quantitative analysis conducted by the committee charged with examining the Institute's training programs found that 17 percent of T32 awardees moved on to receive NIH research support. Many T32 awardees found other ways to contribute to science. For example, up to 50 percent of T32 awardees had published in the last 5 years. Dr. Carter highlighted the following challenges associated with the T32: (1) defining areas where T32 support addresses critical needs, (2) focusing NIAMS T32 investment on high-yield trainees, and (3) maintaining an open funnel to attract new investigators at the upstream end of the research career pipeline.

The following three proposals were put forth:

- *Proposal 1: Define Goals.* Success is defined as T32 trainees advancing to further career development, perhaps through K or F series awards, and develop into independent, funded researchers in an academic setting, or become critical contributors to basic or clinical research teams (i.e., not necessarily as an independent researcher).

- *Proposal 2: Pre-Doctoral Trainees.* For proposals that include support for pre-doctoral Ph.D. candidates, the NIAMS T32 will give preference to T32 programs that provide support for graduate students in Ph.D. programs that provide cross-disciplinary training. The NIAMS T32 will support research opportunities for M.D. students, including doctoral research for M.D./Ph.D. students.

- *Proposal 3: Post-Doctoral Trainees.* Continue to provide research training for those with clinical degrees, and continue to support research opportunities in NIAMS mission areas for those with doctoral degrees, but focus that support.

Dr. Carter further explained that for T32 training programs that propose support for research training as part of a postdoctoral clinical training program, the NIAMS will give preference to programs that provide support for research training that goes beyond the training required for all clinical trainees in that program. For those T32 programs that include Ph.D. trainees, the NIAMS will give preference to those programs in which Ph.D. post-doctoral trainees complete 1 year of post-doctoral training in the laboratory of the proposed mentor before becoming eligible for T32 support. The idea is that the overall level of support that the Institute will provide to a program or institution would remain the same, but the candidate would be asked to show a commitment to NIAMS-related research before becoming eligible.

Discussion

Dr. Jacobs asked about Proposal 2, noting that it singles out M.D. students; he asked about the case of a D.D.S. student who is interested in bone research. Dr. Carter clarified that all the

clinical degrees are included in Proposal 2. Dr. Jacobs suggested that this be specified in the proposal.

Dr. Weinstein noted that the public perception of success is important. In terms of the NIH or Congress, many M.D.s have been funded and received additional degrees in non-specialty areas of health services research. These individuals have been extremely successful as leaders in changing the dynamics of, for example, the orthopaedic profession and understanding health care delivery. The impact on the day-to-day lives of patients may be greater than anticipated. Translating this into the definitions of success is a challenge. This is a highly competitive program, with approximately 450 applications for 4 slots. Dr. Carter noted that it is recognized that there are other ways to make contributions. Ultimately, it will fall to the study section to determine the contribution of the previous trainees that have been supported by a particular program. Some metrics are needed, however, which is why NIH funding and publishing papers were selected. Study sections should have latitude to consider other types of contributions as well. Dr. Katz added that these candidates are extremely talented individuals. Teamwork, for both basic and clinical projects, is important. Having NIH funding also is important; it demonstrates some measure of success in generating new knowledge.

Dr. Kronenberg suggested that the 17 percent success rate associated with T32 awardees moving on to receive NIH funding is indicative of failure. He asked how the T32 compares to the F32s, which are individual awards. Dr. Katz noted that the success rate for the F32s is significantly higher. Dr. Kronenberg commented that a training program should at least match the F32 success rate to consider itself successful. He suggested that if the T32s cannot match the success rate of individual awards, they should be closed; with the T32s, the Institute is trying to train investigators, not support clinical professions. Dr. Katz commented that the F32 payline is very good. Consideration needs to be given to the fields being addressed here, and Dr. Katz suggested that T32s and F32s cannot be equated. F32s involve Ph.D. scientists rather than M.D. scientists. Many of the Institute's training grants are in rheumatic diseases and skin diseases, those are inherently very clinical specialties, and it is a significant challenge to attract research trainees into this process. Dr. Katz added that the Institute faces a much greater challenge than some of the other ICs with respect to its training areas. Dr. Kronenberg suggested that perhaps NIAMS training programs should be smaller and only fund those who will succeed. Dr. Katz noted that the difficulty lies in identifying who is going to be successful compared with who will not.

Dr. Crofford commented that without these training programs, attracting new investigators will be difficult. Ideally, the Institute will be able to create a system of measuring success and creating a scenario in which it invests only in the right people. She suggested that more training programs with more flexibility for institutions could help. Dr. Carter explained that the T32 provides a base that, in rheumatology for example, is critical for allowing a research program for clinical trainees.

Dr. Griffith noted that for many of the cross-disciplinary T32s, in her experience she has found that many of the students are engineering students who move to careers in industry where they are not publishing as much or competing for grants, so it is difficult to interpret the program's

success. Dr. Carter agreed, but clarified that different fields have their own mechanisms for training and that the NIAMS T32 program is geared more for academic researchers.

Dr. Caughman noted that Proposal 3 addresses concerns related to whether or not the candidate is serious and committed, and whether the Principal Investigator (PI) is really invested. In terms of cross-disciplinary team-based science, having a funding source in hand to put a great candidate in a laboratory that is outside of what is traditional in his or her discipline is an effective incentive to get both the candidate and outside PI together. This type of approach is not possible with mechanisms such as the F32. Council member Dr. H. Lee Sweeney, the William Maul Measey Professor and Chair in the Department of Physiology at the University of Pennsylvania School of Medicine, suggested that some of the reasons that the T32s may not do as well include that the large ones are used by institutions for students who are not sure of their career goals. Trying to change the ways institutions use these awards will change the success rates. The inclusion of fellows also hurts the T32 success rate.

VII. R21 PROGRAM

At the last Council meeting, NIAMS' participation in the R21 Program was discussed. Dr. Glen Nuckolls provided a follow-up presentation that incorporated Council input. He reminded members of the two questions guiding the discussion:

- Should the NIAMS continue to participate in the NIH-wide R21 program?

- What steps should the Institute take to encourage and support exploratory projects of high innovation and potential impact?

Dr. Nuckolls reminded the Council that there has been a dramatic increase in the number of R21 applications in the past 6 years, and the NIAMS must consider a balance in funding R21, R01, and other activities. Some NIAMS R21 awards support meritorious projects that do not meet the criteria of highly innovative, ground-breaking research. New and experienced investigators may need additional guidance from the NIAMS in choosing between the R21 and other activity codes.

At the last Council meeting, the following options were presented: (1) no change, continue to participate in the parent R21; (2) the NIDDK model, use the parent R21, but better educate applicants and reviewers, and make more stringent funding decisions; (3) issue an RFA (in place of the parent), emphasize innovation, screen applications for responsiveness; and (4) drop the parent announcement, only use the R21 for occasional research topic-specific announcements. Dr. Nuckolls explained that based on Council discussion and program feedback, it was decided to remove options 1 and 4; the Institute wants to continue use of the R21 but make some changes. Further, the NIAMS has decided to proceed with option 2 (the NIDDK model) because it is believed that with more effective communication with the investigators prior to the application, it is more likely that more appropriate applications and more desirable grants will ensue.

In proceeding with option 2, now known as the NIAMS High Innovation (HI) R21 model, the Institute signed on to the renewal of the NIH parent R21 effective May 16, 2009 – May 8, 2012. Through its Web site (and possibly an announcement in the *NIH Guide*), the Institute will reinforce the goal of supporting highly innovative, ground-breaking research through R21 grants. Potential applicants will be strongly encouraged to discuss their projects with a NIAMS Program Director before applying. Dr. Nuckolls explained that the NIAMS will no longer have a payline for R21 applications. Funding decisions will be made for each application, considering responsiveness to the HI-R21 program and the recommendation of the Program Director.

The message to applicants and reviewers is now that the NIAMS uses the R21 to support projects within its research mission that are: (1) innovative, ground-breaking projects with potential for significant impact; (2) projects that involve novel technology or tool development that have the potential of significantly accelerating research fields; and (3) projects that propose the novel application of methods, technologies, or conceptual approaches from outside biomedical science to a problem in the NIAMS mission. Dr. Nuckolls stressed that projects not suitable for the HI-R21 include projects to develop preliminary data for longer-term projects in a well-established research area, new investigator starter grants, and/or pilot projects that are less than highly innovative.

Preference in funding decisions for R21 grants will be given to projects within the NIAMS mission areas that are especially innovative, ground-breaking and have a high potential impact on these fields. Projects of limited time and scope that do not meet these characteristics of innovative, ground-breaking research should consider applying for a small research project grant (RPG). New investigators are encouraged to apply for an R01 or R03 grants.

Discussion

Council member Dr. Clifford Rosen, Director of Translational Research at the Maine Medical Center, voiced support for the Institute's direction with regard to the R21 mechanism. He emphasized that education is the most important component of this revision, educating not only new investigators but established investigators. He also suggested that professional societies receive this message and that reviewers be informed of the new HI-R21. Dr. Katz agreed, noting that the education component represents a significant challenge. Dr. Kathleen Green echoed Dr. Rosen's comments, stressing the importance of making the Chairs of study sections informed of the HI-R21. She also noted that often, newer members of study sections are not fully familiar with the intricacies of the various funding mechanisms.

Dr. Katz reiterated that the Institute pays special attention to any applications pointed out by the Council, particularly those that are beyond the payline but, based on Council input, should be given a second look. Council input is critical in these matters. Dr. Rosen indicated that NIAMS' revised R21 is a beneficial move for new investigators, particularly if they can be pushed to think in terms of R01s rather than R21s, because there continues to be a misperception that new researchers can enter the system through the R21 mechanism without preliminary data. Dr. Katz agreed, noting that this shift will significantly affect the recent exponential growth in the number of R21 applications seen by the Institute. Dr. Kathleen Green suggested that this topic would be appropriate for inclusion in the Institute's newsletter.

VIII. UPDATE: NIAMS LONG-RANGE PLAN

Anita Linde, Director of the NIAMS OSPP, provided an update to the Council on the Institute's long-range plan covering FY 2010-2014. She reviewed the purpose of the plan, which is to: (1) identify the needs, opportunities, and challenges of the NIAMS; (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. She emphasized that the long-range plan for FY2010-2014 is not meant to replace the previous plan. The long-range plan will include the following five overarching broad topic areas:

- Musculoskeletal biology and diseases
- Bone biology and diseases
- Muscle biology and diseases
- Arthritis and rheumatic diseases
- Skin biology and diseases.

There are a number of sub-topic areas included in the plan, including mechanisms; developmental biology, regenerative medicine, and stem cells; imaging and biomarkers; model systems and therapy development; and clinical research. In addition, three areas have emerged as cross-cutting topic areas to be incorporated into the plan: (1) health disparities, (2) infrastructure, and (3) training and career development.

Ms. Linde presented a timeline for the development process for the long-range plan. A draft of the plan will be presented to the Council for review and comment in August. The September Council meeting will feature additional discussion on the plan. Additional input from NIAMS coalition representatives will be sought in November; the draft plan will be posted online for public comment on the NIAMS Web site in November/December. The final plan will be presented to the Council and posted online in February 2010.

Discussion

Dr. Kronenberg suggested that lessons learned from the current long-range plan that is in effect (covering the years 2005-2009) could be used to help inform the development of the 2010-2014 long-range plan. Ms. Linde indicated that this is the case, and that some of the themes from the previous plan will carry over, while others will not. Dr. Katz clarified that there are differences between IC strategic plans and long-range plans. Strategic plans dictate what an IC will do. Long-range plans define for the community the breadth of the Institute's interest areas, without precluding moving into other areas of scientific importance to the Institute.

Dr. Weinstein discussed the ability of the NIAMS to capture resources across the country where investigators interested in disease could gain use of tools to help the Institute's mission. He asked how long-range planning considers these types of issues. Dr. Katz indicated that long-range planning encourages and embraces this type of activity.

Before moving the agenda forward, Dr. Katz provided some additional data related to the T32 program. For 2007, 24 percent of the 262 individuals receiving T32 training grants were pre-docs. In 2008, 25 percent were pre-docs. In 2007, 18 percent of total dollars went to pre-docs compared with 23 percent in 2008.

IX. NIAMS SCIENTIFIC PLANNING RETREAT

Dr. Katz noted the Institute's appreciation for the attendance and input of Council members Drs. Linda Griffith, Cliff Rosen, and Betty Diamond at the NIAMS Scientific Planning Retreat, held April 6-7, 2009. Dr. Carter summarized the discussion on B cells in autoimmune diseases. Discussion topics included the following: (1) B cell variability in patients (healthy, sick, and undergoing treatment); (2) B cell reconstitution after therapeutic depletion; (3) the effect of immune cell/immune system genetic polymorphisms; (4) animal models; (5) the role of B cells in autoimmune diseases, other than autoantibody production; and (6) the potential for therapeutic B cell modulation. During these discussions, the following needs and opportunities were identified:

- Standardizing B cell subsets
- Devising methodologies for identifying antigen-specific B cells in disease
- Employing novel approaches to understanding B cell behavior (i.e., encouraging the development of advanced technologies)
- Reassessing clinical research endpoints (i.e., supporting rituximab trials in patient subsets of lupus and other rheumatic diseases).

Dr. Diamond, Chief of the Laboratory of Autoimmune Disease at the Feinstein Institute of Medical Research, added that much of the discussion focused on the failure of the large rituximab trial to move the field forward. Dr. Katz noted that of particular interest is whether the trial was not as successful as hoped because of the instruments used or because of the drug.

Dr. Griffith then reviewed the discussion on stem cells that occurred during the Retreat. Major discussion topics on this theme included the state of the science, common themes among stem cell applications, understanding stem cell growth and behavior, therapy delivery, immune response and other complications, and unanswered questions. The following needs and opportunities were identified during the discussions:

- A better understanding of stem cell behavior, from culture to the human body

- Cross-disciplinary collaboration (with a focus on clinical research training)

- Standardization (both techniques and protocols)

- Animal models (especially developing and paying for large animal models).

The Retreat also featured a discussion on the challenges facing the Institute. Dr. Carter reported that preliminary input from Retreat participants related to two key questions: (1) What major scientific challenges face the NIAMS scientific community? and (2) How can the NIAMS help its community to overcome them? The following main discussion questions were developed:

- What are the resource and infrastructure challenges?

- How can the NIAMS ensure that the investigative groups supported by the Institute are availed of emerging technologies?

- How can the NIAMS best continue its commitment to basic discovery?

Dr. Carter explained that the key discussion points focused on resources and infrastructure (including conference grants, biomarkers, and registries); emerging technologies (e.g., the need for standardized processes, the value of centralized access, the promotion of cross-disciplinary teams, and NIAMS' role in promoting resource availability); and the Institute's commitment to basic discovery (e.g., encouraging interactions between researchers, supporting small meetings representing various disciplines, and peer review within the context of high-risk research).

X. FUTURE APPROACHES TO NIAMS CLINICAL TRIALS

The fourth main area of discussion at the April NIAMS Scientific Planning Retreat involved future approaches to NIAMS clinical trials. Dr. Joan McGowan explained that the goals of this session were to increase the impact and quality of clinical trials supported by the Institute. After the Retreat and ensuing discussions among the NIAMS Clinical Trials Working Group, Council input is being sought to determine next steps. Dr. McGowan explained that the NIAMS investment in clinical trials increased significantly with the doubling of the NIH budget. A recent Institute review of the currently funded studies suggested the need to examine: (1) the identification of opportunities and priorities for the NIAMS clinical trials portfolio, and (2) approaches for implementing and facilitating high-quality trials. Dr. McGowan emphasized that the NIAMS will continue to solicit input from the extramural scientific research community.

Since the doubling of the NIH budget, starting in about 1999, NIAMS has increased the percentage of its overall budget dedicated to clinical trials. The Institute is proud of its investment in these trials, and is looking to improve this investment. Currently, there are approximately 46 funded trials at the NIAMS. Of these, roughly 10 percent were solicited, through broad agency announcements; the remaining 90 percent were unsolicited (i.e., investigator-initiated). Approximately 70 percent of the unsolicited trials are under $500,000. Dr. McGowan noted that there is no pre-approval process for applications under $500,000.

The goals of the discussion session at the Retreat as related to NIAMS clinical trials were to explore and analyze some approaches that the Institute can use to more effectively identify, solicit, support, and manage high-quality and significant clinical trials. At the retreat, participants examined and discussed a variety of models used by the other NIH Institutes to accomplish these goals.

Dr. McGowan asked Council members to consider whether the Institute should implement any new strategies for clinical trials selection and implementation to support trials of higher impact and quality. Council members were asked specifically about the identification of opportunities for Institute and investigator-initiated trials. Engaging scientific organizations, networks and research centers, advocacy groups, and the private sector is important. Dr. McGowan asked, in terms of the clinical trials research portfolio, if there are additional specific activities in information gathering that the Institute can engage in to ensure that it is supporting the best and most important high-impact trials. This activity is an adjunct to the Institute's normal planning process. Dr. McGowan asked for Council input on whether it might make sense to establish NIAMS external advisory groups and/or a subcommittee of the Council to consider identifying these clinical trials.

Dr. Katz explained that currently, the Institute has to accept any trials for review that come in for funding at less than $500,000 per year. One option may be to institute a planning process before such a review begins. Dr. Rosen pointed out that in almost every circumstance, $500,000 per year for a clinical trial is unlikely. Dr. Weinstein referred to a study looking at burden of disease and disability-adjusted life years (DALYs) within the context of NIH funding over several years. Musculoskeletal topics were not included as a topic for analysis; Dr. Weinstein suggested that future similar trials include musculoskeletal topics as well. He also reiterated that the planning process is incredibly useful for the Institute and is an effective way to identify projects that may not warrant consideration for a real trial. Dr. Katz commented that burden of disease is a difficult and somewhat subjective issue to analyze and incorporate in a study.

Dr. Kronenberg expressed surprise that 70 percent of clinical trials funded by the Institute are unsolicited, investigator initiated, and less than $500,000 per year. He asked how many of these studies surprised Institute leadership in terms of topics, ideas, or approaches. Dr. McGowan noted that clinical trials, by their nature, cannot be too surprising because some degree of groundwork has to be carried out. One of the major observations in looking at these trials that came in under $500,000 is that in many cases, they were submitted by naive investigators who did not know what it takes to enroll patients into a trial and other issues.

Dr. Jacobs noted that in terms of identifying opportunities, the ability of professional organizations and specialty societies should be drawn on. These are the people in the field who know what the issues are, what the important clinical questions are, and what needs to be done. Obtaining broad input from a wide variety of organizations would be helpful. He added that the American Academy of Orthopedic Surgeons and the U.S. Bone and Joint Decade have tried to define and quantify the "burden of disease." Their definition may be of some use to the Institute. Dr. Jacobs asked about how the Institute was defining clinical trials for the purposes of this discussion. Dr. McGowan indicated that a clinical trial involves an intervention with a placebo,

typically in these cases involving hundreds of patients. Dr. Jacobs noted that burden of disease should not be the only consideration, but should be one of them; Dr. Katz agreed.

Dr. Kronenberg suggested that new study sections could be formed to focus on clinical trials and expressed support for having the majority of clinical trials being investigator initiated. Dr. Crofford asked if the Institute's evaluation of its clinical trials portfolio included engaging investigators in networks and yielded studies that had good success rate and impact. If so, the Institute could consider utilization of some of these networks to facilitate the receipt and support of high impact clinical trials.

Dr. Weinstein noted that in the case of uncommon disease entities, study design matters; there are ways to conduct cluster-type studies on a national basis that allow rarer diseases to be studied fairly effectively and quickly.

Dr. McGowan then moved the discussion to focus on investigator-initiated clinical trials. She explained that investigator-initiated clinical trial applications with budgets greater than $500,000 per year have acceptance criteria that include relevance to the Institute's mission, evidence of feasibility, and budget. As noted previously, applications under $500,000 are all accepted as long as they are within the mission of the NIAMS. Investigator-initiated applications come into the Institute as R01s; they can be changed to Cooperative Agreements as needed. Most investigator-initiated applications are reviewed by the Center for Scientific Review, and planning grants/phases are not required.

Dr. McGowan presented the following three options for discussion: (1) no change in the Institute's approach to investigator-initiated clinical trials, (2) supporting solicited clinical trials (RFPs or RFAs only), and (3) structuring the process by expanding the use of the planning grants or similar structured planning phases for all clinical trials and manage them by cooperative agreements. It was decided to take the first option (no change) off the table. Dr. McGowan noted that there are advantages and disadvantages associated with the second option (supporting solicited clinical trials only). Advantages include the fact that this approach allows for the greatest concentration of resources in selected areas of greatest need and feasibility. In addition, use of the contract mechanism allows for great cost accountability. The disadvantages, however, are that this approach may not effectively capture emerging opportunities and narrows the areas of investigation.

The third option, which involves structuring new investigator-initiated applications for clinical trials, could proceed through a two-part process. First, a planning grant would be a prerequisite for submission of a multicenter clinical study (funding the planning grant would not commit the NIAMS to funding the actual trial). Second, trials would be submitted using the Cooperative Agreement mechanism and would require NIAMS pre-approval. The NIAMS is considering use of the planning grants in this context for a number of reasons. For example, they: (1) permit early peer review of the rationale for the proposed study, (2) assess the design and recruitment of the study, (3) support the development of a protocol and manual of operating procedures, and (4) provide support for other elements of coordination and decision making necessary to the conduct of a high-quality study. Dr. McGowan then explained the rationale for potentially using Cooperative Agreements for multicenter clinical studies. This approach allows the Institute to

accept, peer review, and consider funding applications from planning grant awardees only. There would be substantial involvement with the grantee during the conduct of the clinical study, without assuming direction of the study or a dominant role.

Dr. Weinstein suggested incorporating a plan for data capture and management in the planning grant. Dr. Diamond commented that it is critical that there be a pre-review of clinical trial proposals. She also suggested that the Institute adopt an approach that allows it to be more selective (i.e., vetting proposals prior to accepting them for review). Dr. McGowan clarified that some manner of opt-out option for the planning grant would be available in situations for which the planning grant requirements have already been met through another IC's funding, a separate planning process, or a network. Dr. Katz indicated that the third option presented by Dr. McGowan would eliminate some of the downstream clinical challenges in starting a clinical study by having more interaction up front. Dr. Rosen added that this approach encourages the investigator to come to the NIAMS and say "this is what I want to do and how I want to do it, how do I go about it?" rather than a *de novo* clinical trial grant arriving at the Institute after peer review.

Council member Ms. Patricia McCabe Estrada, a patient advocate, expressed support for the third option. She noted that it makes sense to take a slow, careful approach at the outset before a trial gets underway. Dr. Katz summarized that more interaction up front does not in any way preclude an investigator from submitting an application; however, this approach does require that investigator to carry out some up-front work to prevent wasting time in getting the study going and prevent the submission of proposals that will not be successful.

XI. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 635 applications in closed session requesting $142,954,834 and recommended 635 for $142,954,834.

XII. BOARD OF SCIENTIFIC COUNSELORS

This presentation was given during closed session.

XIII. ADJOURNMENT

The 68th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 2:30 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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