National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

January 29, 2008

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

MINUTES OF THE 64th MEETING

January 29, 2008
8:30 a.m. to 4:00 p.m.

I. CALL TO ORDER

The 64th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on January 29, 2008, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 6. The meeting was chaired by Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Attendance

Council members present:

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

Council members not present:

Dr. Kevin Campbell

Staff and Guests:

The following NIAMS staff and guests attended:

Staff

Mr. Steven Austin
Dr. Carl Baker
Ms. Susan Bettendorf
Dr. Michael Bloom
Dr. Amanda Boyce
Dr. Eric Brown
Dr. Branden Brough
Ms. Justine Buschman
Mr. Richard Clark
Ms. Robin Diliello
Ms. Teresa Do
Dr. Jonelle Drugan
Mr. Erik Edgerton
Ms. Sharon Fair
Ms. Barbara Footer
Ms. Gail Hamilton
Ms. Jane Hymiller
Dr. Stephen Katz
Ms. Shahnaz Khan
Ms. Stephanie Kreider
Dr. Cheryl Lapham
Dr. Gayle Lester
Dr. Helen Lin
Ms. Anita Linde
Ms. Mimi Lising
Ms. Elizabeth Lordan
Dr. Kan Ma
Dr. Marie Mancini
Dr. Kathryn Marron
Dr. Joan McGowan
Ms. Leslie McIntire
Ms. Amy Melnick
Ms. Melinda Nelson
Dr. Steve Nothwehr
Dr. Glen Nuckolls
Dr. James Panagis
Ms. Wilma Peterman Cross
Dr. Paul Plotz
Ms. Trish Reynolds
Dr. Louise Rosenbaum

Ms. Karin Rudolph
Dr. William Sharrock
Dr. Lawrence Shulman
Ms. Sheila Simmons
Dr. Susana Serrate-Sztein
Ms. Theresa Smith
Ms. Allisen Stewart
Ms. Robyn Strachan
Ms. Cassie Terra
Ms. Yen Thach
Mr. Michael Toland
Dr. Madeline Turkeltaub
Dr. Bernadette Tyree
Dr. Fei Wang
Dr. Ping Wang
Dr. Yan Wang
Dr. Chuck Washabaugh
Mr. Elijah Weisberg
Ms. Sara Wilson
Dr. James Witter

Guests

Dr. Toby Behar, Center for Scientific Review, NIH
Mr. Michael Bykowski, Consolidated Solutions and Innovations
Dr. David Cella, Evanston Northwestern Healthcare
Ms. Diane Christianson, Society for Investigative Dermatology
Ms. Ann Elderkin, American Society for Bone and Mineral Research
Ms. Christy Gilmour, American Academy of Orthopaedic Surgeons
Ms. Hilary Hansen, National Psoriasis Foundation
Dr. Timothy Hayes, Office of Portfolio Analysis and Strategic Initiatives, NIH
Ms. Jennifer Isenberg, IQ Solutions
Ms. Alicia Lawson, National Institute on Aging, NIH
Dr. Vivian Pinn, Office of Research on Women's Health, NIH
Dr. Jennifer Pohlhaus, Office of Research on Women's Health, NIH
Ms. Joyce Rudick, Office of Research on Women's Health, NIH
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 63rd Council meeting, held on September 27, 2007.

III. FUTURE COUNCIL MEETING DATES

Future Council meetings are currently planned for the following dates:

June 6, 2008
September 23, 2008
February 3, 2009
June 2, 2009
September 16, 2009

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz welcomed Council members, NIAMS staff, and guests. He began his report by inviting them to review the NIAMS Shorttakes online, which include more detail on many of the topics covered in his report. He noted that his Director's Column focuses on an outreach event that was organized by the Institute in December for members of the NIAMS Coalition. Almost 40 Coalition groups participated in the event to network with each other and learn more about NIAMS' programs and priorities. Dr. Katz thanked Dr. Janet Austin and Betsy Lordan from NIAMS' Office of Communications and Public Liaison (OCPL), as well as Wilma Peterman Cross from NIAMS' Office of Science Policy and Planning for developing the program. He reminded Council members that the Shorttakes newsletter provides a wealth of information on recent scientific advances, research funding opportunities, and staff changes.

Before beginning his formal remarks, Dr. Katz welcomed the following incoming Council members (these individuals served as *ad hoc* Council members during the meeting):

John H. Klippel—Dr. Klippel is President and Chief Executive Officer of the National Arthritis Foundation, the largest health voluntary organization in the United States serving people with arthritis. Prior to joining the Foundation in 1999, he served as the Clinical Director of the NIAMS Intramural Research Program. Dr. Klippel is a Fellow of the American College of Physicians and American College of Rheumatology, and has received numerous honors and awards, including the Surgeon General's Exemplary Service Award.

Ann Kunkel—Ms. Kunkel is the Education Coordinator in Pediatric Rheumatology at the University of Kansas Medical Center, and a prominent volunteer for the Arthritis Foundation and the Association of Rheumatology Health Professionals. She has been an effective advocate for support of medical research and health care services for patients affected by rheumatic diseases, and has received numerous awards for her efforts, including the Charles B. Harding Award for Outstanding Volunteer Service from the national Arthritis Foundation.

H. Lee Sweeney—Dr. Sweeney is the William Maul Measey Professor and Chairman of the Department of Physiology, and Professor of Medicine and Professor of Surgery at the University of Pennsylvania School of Medicine. An internationally renowned expert in the fields of muscle physiology and muscular dystrophy, Dr. Sweeney is a member of many professional organizations, including the Biophysical Society and the American Society for Cell Biology. He

also is a former member of the Board of Scientific Counselors for the NIAMS Intramural Research Program.

S. Wright Caughman—Dr. Caughman is the Executive Associate Dean for Clinical Affairs at the Emory Clinic, and the Alicia Leizman Stonecipher Chair in the Department of Dermatology at the Emory School of Medicine. Dr. Caughman is widely published in the dermatology and immunology fields, and is a member of numerous professional societies, including the Society for Investigative Dermatology, the American Academy of Dermatology, and the American Association for the Advancement of Science.

Personnel Changes at the NIH and NIAMS

At the NIH level, Dr. Josie Briggs has been named as the new Director of the National Center for Complementary and Alternative Medicine.

At the Institute level, the search continues for a Deputy Director. Council members were asked to forward any suggestions of individuals for this role to Dr. Katz. NIAMS welcomes Ms. Sara Rosario Wilson, who joined OCPL as a Multi-Cultural Health Educator. Ms. Wilson comes to the NIAMS from the National Institute on Drug Abuse. In the NIAMS Extramural Program, Dr. Yan Wang has been selected as a Program Director in the Division of Skin and Rheumatic Diseases. Dr. Wang served as Chief of the NIAMS Scientific Review Branch for the past several years. Ms. Barbara Footer has joined the NIAMS Extramural Program as a Research Program Analyst in the Division of Skin and Rheumatic Diseases. Before joining the Institute, Ms. Footer worked with the State of New Mexico managing behavioral health grants. Dr. Debbie Stone has joined the NIAMS Intramural Research Program as a staff clinician in the Office of the Clinical Director. Dr. Stone is a pediatrician and will help manage NIAMS' extensive pediatric program on autoinflammatory diseases.

Update on Budget

In Fiscal Year 2007 (FY 2007), the NIAMS funded 261 new and competing continuation applications for a success rate of 20 percent; the overall NIH success rate was 21.3 percent. Additional details about the distribution of the FY 2007 appropriation, including success rates for all budget activities, are available on the NIAMS Web site.

For FY 2008, President Bush signed into law the Consolidated Appropriations Act (Public Law 110-161, HR 2764) on December 26, 2007. The law provides $29.5 billion for the NIH, following an across-the-board rescission of 1.7 percent. This represents an increase of approximately 1 percent over FY 2007. Similar to last year, the appropriation to the NIH Office of the Director includes funding for the NIH Common Fund, which includes the NIH Roadmap. The funding level for NIAMS in FY 2008 is $508.6 million, which is essentially level with FY 2007. Dr. Katz noted that the omnibus bill included a provision which mandates that investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts, to be made publicly available no later than 12 months after the official date of publication, in a manner consistent with copyright law.

Dr. Katz reported that specific funding policies are still being developed within the NIH and will be shared when available. The NIAMS will be funding research project grant (RPG) applications at a payline of 14.5 percent and will have an average downward negotiation of 12 percent (less than last year's 14 percent). For new investigators, the payline will start at 17.5 percent. All R-21 awards will be funded at the same payline as RPG awards (14.5 percent). Institute policy for non-competing awards allows a 1 percent inflationary increase for non-competing grants. Dr. Katz noted that a discussion point for a future Council meeting may be how best to prevent eroding good science while encouraging more new applications to sustain the research enterprise given the current budget constraints. Dr. Katz added that the President's Budget request for FY 2009 is scheduled to be released on February 4th; details will be shared after that date.

Highlights of Selected Recent Scientific Advances

Before describing specific studies, Dr. Katz commented that there have been major advances in lupus genetics and therapy. Identifying genetic susceptibility markers to rheumatic diseases has reached a "fever pitch" in the last few months, with the refinement of tools for genome-wide association and genetic linkage studies. Several articles from projects with NIAMS support have been published about genetic associations with systemic lupus erythematosus (SLE) in high-profile journals. Genome-wide association, linkage analysis, and direct sequencing were used in large, case-controlled studies; several findings were replicated in distinct racial or ethnic populations. Many single nucleotide polymorphisms (SNPs) confirmed previously identified SNPs associated with immune regulation, such as histocompatibility molecules, STAT4, and interferon regulatory factor 5. New SNPs from these reports occurred in molecules involved in vascular cell adhesion, clearance of immune complexes, and immune cell development and maturation. Disease-associated alterations in the gene products may contribute to vascular complications, persistence of inflammatory stimuli, and impaired tolerance mechanisms, leading to autoimmunity. As noted in an accompanying editorial by Dr. Peggy Crow in the *New England Journal of Medicine*, a critical factor in these and future studies is the collaboration between U.S. and European researchers, supported by government agencies, private foundations, and industry. Dr. Katz noted that the investments in these efforts started 10-12 years ago.

NIAMS-supported researchers have developed new tools that may facilitate the use of biologics to treat systemic lupus erythematosus (*J Immunol.* 2007 Sep 1;179(5):3351-61). Most of the current lupus therapies are not effective in controlling disease or preventing permanent organ damage. In addition, they have significant and sometimes dangerous side effects, such as increasing the risk of osteoporosis and cardiovascular disease. B cells are immune system cells that drive the production of antibodies—autoantibodies in lupus—and B cell depletion holds promise as a potential lupus treatment. Anti-human-CD20, also known as rituximab, significantly reduces B cell populations by attaching to a molecule, CD20, found on the surface of human B cells, and is a current, approved treatment for diseases such as non-Hodgkin's lymphoma and rheumatoid arthritis. Dr. Mark Shlomchik from the Yale University School of Medicine and colleagues created an important mouse model of lupus that responds to B cell depletion with clinical improvement; this is an important step in understanding the mechanisms of this treatment before clinical testing in humans.

Following these remarks, Dr. Katz described additional recent scientific advances:

- A mouse model of the human skin disease epidermolysis bullosa (EB) simplex was developed by knocking out the gene for keratin 14, a skin protein that participates in mechanical support for cells. Further studies identified sulforaphane, a natural product from broccoli sprout extract, as a potential therapeutic. Sulforaphane provides anti-oxidant and anti-carcinogen protection, and stimulates other keratin genes, via a cell communication pathway, resulting in production of keratin proteins in the EB simplex mouse model that compensate for the lack of keratin 14. The skin fragility and blistering in this mouse model was prevented by injecting sulforaphane into pregnant mothers shortly before birth, followed by topical sulforaphane treatment of the newborn mice. This exciting work by Dr. Paul Talalay of the Johns Hopkins University School of Medicine and colleagues suggests that small molecule drugs may be promising medications for some forms of EB and other inherited skin diseases (*PNAS* 2007 Sep 4;104(36):14460-5. Epub 2007 Aug 27).

- A new study provides better understanding of the pigmentation process and of the determinants of pigmentation patterns. Pigmentation of skin and hair plays an important role in protection from ultraviolet light damage and can have profound influences on social interactions. Dr. Janice Brissette, from the Massachusetts General Hospital and Harvard Medical School, and colleagues discovered that the hair follicle and epidermis of the skin have dedicated pigment recipient cells that direct the pigment donor cell, the melanocyte, where to migrate and where to deposit its melanin pigment. In addition, they identified specific messenger molecules that facilitate melanocyte recruitment and melanin transfer. Studies such as this one provide potential targets for the manipulation of pigmentation and the correction of pigmentation defects in disorders such as vitiligo (*Cell*. 2007 Sep 7;130(5):932-42).

- Researchers now have direct evidence that when someone aged 65 years or more appears at a doctor's office or hospital emergency department with a broken bone, that person should be screened for osteoporosis—even if the fracture occurred because of a highly traumatic injury that could hurt even a healthy younger person. Although clinicians are quick to recognize osteoporosis as the cause of fractures resulting from minimal insult, breaks related to more substantial injury rarely are attributed to underlying bone disease. The latest findings, which come from the longstanding NIAMS-funded Study of Osteoporotic Fractures and Osteoporotic Fractures in Men Study (MrOS), revealed that older people who suffer high-trauma fractures are likely to have low bone mineral density and are at increased risk of subsequent fractures. They lend further credence to a recommendation, outlined in the Surgeon General's 2004 report on Bone Health and Osteoporosis, that fracture patients over 50 years of age should be tested for osteoporosis and, if found to have low bone mass, should take various steps to protect their bones (*JAMA*. 2007 Nov 28;298(20):2381-8).

- Council member Dr. Cliff Rosen, Executive Director of the Maine Center for Osteoporosis Research and Education, and colleagues recently published a paper in the *Proceedings of the National Academy of Sciences* that adds to a growing body of evidence that bone and fat are, in fact, closely linked. Their data, which show that a 15 minute exposure to low-magnitude mechanical signals each day suppresses fat mass in normal mice and in a strain genetically

predisposed to develop obesity, could have implications for the design of therapeutic strategies for a wide range of public health problems, including osteoporotic fracture and cardiovascular disease. In addition, the evidence suggests that the many health benefits of physical exercise, sometimes thought of as arising simply from the burning of excess calories, may actually reflect a complex network of specific biochemical responses in many different tissues (*PNAS*. 2007 Nov 6;104(45):17879-84. Epub 2007 Oct 24).

- New findings by Dr. David Felson from the Boston University School of Medicine and colleagues suggest that an elevated blood level of cartilage oligomeric matrix protein (COMP) fragments—a byproduct of cartilage degradation—is predictive of osteoarthritis (OA) progression in individuals who already have knee OA. The results were published by the Felson Laboratory, which compared concentrations of candidate biomarkers in blood and urine samples of patients whose condition remained stable over 2.5 years with measurements from those who had progressive joint deterioration. The ability to recognize people in whom osteoarthritis is likely to worsen is essential if the promise of predictive medicine is to be realized. First, the finding that a one-time measurement of COMP fragments in blood serum is associated with a person's risk of additional joint damage will be useful when identifying a subset of patients who might be better suited than others for participation in clinical trials of OA therapies. Second, as researchers develop strategies to halt disease progression, at-risk patients will be able to benefit from early interventions while those who are less likely to be helped will be spared the expense and side effects associated with unnecessary treatment (*Arthritis Res. Ther*. 24:R108 (2007) [ahead of print]).

- Researchers have developed a method of modifying injectable arthritis drugs that should provide for sustained presence of the medication in the joint space. Dr. Lori Setton and her colleagues at Duke University designed a protein fragment that aggregates and remains at the site of the injection. When combined with the target drug interleukin-1 receptor antagonist, the molecules formed drug deposits that slowly released therapeutic molecules. The study was not designed to test the new therapy's effectiveness against arthritis. Its results suggest, however, that the protein complex will increase the duration of drug presence in the joint space and might also reduce negative side effects, since the drug remains at the injection site instead of accumulating in the bloodstream (*Arthritis Rheum.* 2007 Nov;56(11):3650-3661).

- Dr. Martha Murray and colleagues at Children's Hospital Boston recently published findings that enhance understanding of the physiologic differences between the healing responses of injuries to intra-articular and extra-articular ligaments. Her research team examined how cells in various knee ligaments of dogs respond to damage and demonstrated that the inadequate tissue-repair process of the anterior cruciate ligament can be altered to resemble the more effective healing seen in medial collateral and other ligaments. Although extra-articular ligament wounds healed more fully than the ACLs, researchers were able to promote repair during the 6-week study period by inserting a cell-coated protein scaffold into the damaged ACLs—a discovery that may pave the way for biologic or tissue-engineered methods to enhance recovery from common, sports-related ACL injuries (*J. Orthop. Res.* 2007 Aug;25:1007-17).

- Myoblast transplantation is a clinically approved approach for treating a variety of conditions, but the procedure has had limited success because the implanted cells rarely survive and do not spread much beyond where they are injected. While creating mice deficient in various genes involved in muscle development and repair, Dr. Michael Rudnicki of the Ottawa Health Research Institute and colleagues discovered that satellite cells lacking MyoD divided faster than normal cells, but differentiated to a lesser extent. In a follow up to those observations, they recently noted that MyoD-negative myoblasts (compared with unaltered satellite cells) had a gene expression pattern that more closely resembled that of stem cells and, when injected into a mouse model of muscle damage, more readily engrafted into muscle. Furthermore, unlike their unaltered counterparts, the MyoD-negative myoblasts began to rejuvenate the satellite cell population in the damaged muscle (*PNAS*. 2007 Oct 16;104(42):16552-7. Epub 2007 Oct 10).

- Using mice models, NIAMS intramural researchers under the direction of Scientific Director Dr. John O'Shea discovered the pathway by which interleukin 10 (IL-10) is produced. IL-27 and IL-6 induce T cells—a specific immune cell population—to secrete IL-10. Interestingly, the T cells that were found to produce IL-10 are the same that have been known to produce the inflammation-promoting IL-17. Understanding of IL-10 production may give scientists a way to avoid autoimmune disease (*Nature Immunol*. 2007 Dec;8(12):1363-71).

NIH/NIAMS Activities and Plans for the Future

Dr. Katz explained that as part of Roadmap 1.5 activities, efforts are currently underway to solicit applications in the areas of epigenomics and the human microbiome. Next month, Dr. Zerhouni will meet with NIH Institute and Center (IC) Directors to review concepts for potential 2009 Roadmap initiatives. It is anticipated that a select number of such trans-NIH initiatives will be supported through the NIH Common Fund.

As noted at previous Council meetings, NIAMS recently organized the mid-course review of the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative. PROMIS is one of the Roadmap 1.0 projects designed to re-engineer the clinical research enterprise. Dr. Jim Witter of the NIAMS Division of Skin and Rheumatic Diseases recently succeeded Dr. Bill Riley of the National Institute of Mental Health as the Chief Science Officer for PROMIS. During this meeting, Council members were provided with an update on PROMIS (see section VII. THE PATIENT REPORTED OUTCOMES MEASUREMENT IFORMATION SYSTEM (PROMIS): AN NIH ROADMAP INITIATIVE).

Dr. Katz explained that the NIH Reform Act of 2006 established a Council of Councils to: (1) advise the NIH Director on matters related to the policies and activities of the NIH Division of Program Coordination, Planning, and Strategic Initiatives; and (2) make recommendations on the conduct and support of trans-NIH research proposals supported by the Common Fund. Council member Dr. Bevra Hahn, Professor in the Department of Medicine at the University of California, Los Angeles School of Medicine, represents the NIAMS Advisory Council on the group and serves as a liaison between the two Councils. Dr. Hahn participated in the Council of Council's planning meeting on November 8, 2007, and provided Council members with an

update on that meeting later in the agenda (see section V. REPORT FROM THE COUNCIL OF COUNCILS).

Dr. Katz noted that the increasing breadth, complexity, and interdisciplinary nature of biomedical science are creating new challenges for the system used by NIH to support the best biomedical and behavioral research by the best scientists with the least administrative burden. NIH Director Dr. Elias Zerhouni has charged two high-level working groups to examine this issue and make recommendations for enhancing NIH peer review. More information will be presented at the next Council meeting.

A key ingredient in research success is translation of laboratory insights to patient care, and the application of subsequent observations to new laboratory investigations that further improve public health. In this vein, NIAMS launched its Centers of Research Translation (CORT) program and awarded its first round of grants in FY 2006. In FY 2007, the Institute funded a second set of awards, for a total of seven Centers. The Centers run through FY 2011 or 2012, and unite basic and clinical scientists in a way that helps convert research discoveries into new drugs, treatments, and diagnostics.

As part of ongoing efforts to keep the Council apprised of potential scientific initiatives from the NIAMS, Dr. William Sharrock presented a concept for replication of genome-wide association studies in NIAMS mission areas to the Council at this meeting (see section X. NIAMS FY 2009 INITIATIVES). This concept may be pursued as a new initiative in FY 2009.

The Institute is in the process of planning its annual Scientific Retreat; Council members Drs. Wright Caughman, Betty Diamond, and Larry Raisz, and Ms. Ann Kunkel will be attending the meeting.

As a follow-up to the training program evaluation that was discussed at the last Council meeting, the NIAMS is planning a 1-day meeting to explore career path issues for rheumatology researchers in collaboration with key organizations such as the American College of Rheumatology and the Arthritis Foundation. Based on the outcome of this meeting, similar sessions may be organized to cover other disciplines in NIAMS mission areas.

In terms of outreach and dissemination efforts, Dr. Katz drew Council members' attention to several articles in the American Academy of Orthopaedic Surgeon's November 2007 issue of *AAOS Now* that mention the Institute's interest in supporting orthopaedic research. In addition to an interview in which Dr. Katz describes how NIAMS identifies the research projects that it supports, the *AAOS Now* issue also includes articles about training opportunities for orthopaedic surgeons and about how to apply for an NIH grant. The Fall 2007 issue of *NIH Medline Plus: The Magazine* features an article about a partnership with the National Aeronautics and Space Administration (NASA) that NIAMS is developing as part of Dr. Katz's role as NIH liaison to NASA and as a member of the NASA Administrator's Advisory Council. These activities are intended to help American scientists utilize the International Space Station to answer questions about human health and diseases, including musculoskeletal conditions such as osteoporosis and muscle wasting. Dr. Katz recognized Dr. Jonelle Drugan and Ms. Anita Linde of NIAMS' Science Policy Office for their efforts in organizing this new partnership with NASA.

Council members also were provided with two items related to the Institute's bone health efforts: (1) a new Chinese language version of the "People's Piece" from the *Surgeon General's Report on Bone Health and Osteoporosis*, and (2) a 2008 Bone Health Pocket Calendar that provides important information about strategies and resources to maintain a healthy skeleton. Dr. Katz acknowledged Dr. Ping Wang of the NIAMS' OCPL for his work in assisting with the translation of the "People's Piece" into Chinese, which serves as an example of NIAMS efforts to reach diverse populations with important health messages.

V. REPORT FROM THE COUNCIL OF COUNCILS

NIAMS Council member Dr. Bevra Hahn explained that the Council of Councils advises the NIH Director on matters related to the policies and activities of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI). The Council makes recommendations on the conduct and support of trans-NIH research proposals supported by the common Fund. The Council had its first meeting in November 2007. It was formed following the NIH Reform Act of 2006, which passed Congress with virtually unanimous support in December 2006. The act authorizes appropriations for this new structure to facilitate trans-NIH research. Key provisions of the NIH Reform Act include the following:

- Establishes the DPCPSI.
- Establishes the use of the Common Fund.
- Creates the Council of Councils to guide trans-NIH priorities.
- Establishes the Scientific Management Review Board (SMRB) to oversee evaluation or organizational structures and authorities that may be used for improvements.
- Initiates a public process to review potential organizational changes.

The Reform Act represents the first omnibus reauthorization of the NIH in 14 years.

The DPCPSI is authorized to identify trans-NIH research (through the Roadmap process, for example) for support by the Common Fund. Trans-NIH research proposals must include milestones and goals for research activities; appropriate consideration must be given to proposals from first-time NIH investigator applicants. There also is a requirement for the inclusion of information on trans-NIH research in the new *Biennial Report*. Dr. Hahn explained that the Office of Disease Prevention (ODP), Office of Research on Women's Health (ORWH), Office of AIDS Research (OAR) and Office of Behavioral and Social Sciences Research (OBSSR) will be encompassed by the DPCPSI; however, legislation explicitly states that these offices are to retain authorities in effect prior to enactment.

Dr. Hahn noted that the Common Fund is a source of funds for innovative and cross-cutting initiatives that will improve and accelerate biomedical research and its impact on the health of the nation. The Fund is managed by the DPCPSI, and works as the roadmap for the medical research fund (currently 1.7 percent of the NIH budget). The Reform Act does not establish a formula for growth, but the fund cannot drop as a percentage of the NIH budget and review is required when the Common Fund reaches 5 percent of the total NIH budget. Roadmap initiatives, supported by the Common Fund, must demonstrate: (1) high potential to transform how biomedical and/or behavioral research can be conducted; (2) a synergistic promotion and advancement of the missions of the individual Institutes to benefit health, or applicability to issues beyond the scope of any one or a small number of Institutes; (3) a likelihood that no other entity is likely or able to perform the work; and (4) a public health benefit of having the results of the research in the public domain.

Dr. Hahn described the annual process of creating ideas and supporting them through the release of Requests for Proposal (RFP). The Council of Councils is expected to help gather ideas and refine selected ideas that fulfill the criteria she described for the Roadmap. The Council of Councils has also been tasked with addressing problems related to: (1) recognizing innovation; (2) the workforce (e.g., the average age of NIH Principle Investigators (PIs) has increased from 39 years in 1980 to 50 years today); and (3) bridging the sciences. In closing, Dr. Hahn noted that the Council of Councils has established subcommittees focused on resource development and analysis, strategic coordination, and evaluation and systematic assessments.

Discussion

NIAMS Advisory Council member Dr. Joshua Jacobs, an orthopaedic surgeon at Rush University Medical Center, asked how often the Council of Councils meets. Dr. Hahn indicated that the Council will meet quarterly, not including subcommittee meetings. Dr. Katz asked if the Council of Councils has any surgeons as members. Dr. Hahn indicated that she did not immediately know, but would provide Dr. Katz with an answer at a later time.

VI. NIH KNOWLEDGE MANAGEMENT

As part of other efforts to implement the provisions of the NIH Reform Act, the agency is developing a new system to report on spending related to research and disease areas—the Research, Condition, and Disease Categorization (RCDC). Dr. Timothy Hayes, Director of the RCDC Project and Chief of the Portfolio Analysis and Scientific Opportunities Branch within OPASI, characterized the RCDC system as a new process by which the NIH will categorize all of its research (grants, intramural in-house research, research and development contracts) through a semi-automated system in a transparent manner. The current NIH category reporting system lists approximately 240 categories and provides information on how much the NIH spends collectively on each. The system is updated on an annual basis; each IC provides their numbers to the Central Budget Office.

Dr. Hayes explained that every year, the NIH reports to Congress and the public on how much it spends on research and disease areas; this information allows Congress and the public to better

understand NIH research spending and priorities (e.g., to illustrate where the money NIH receives from Congress goes). In 1998, the first of two National Academy of Sciences (NAS) reports addressing this issue at the NIH was released. The first report indicated that the NIH needed to more effectively account for how dollars are spent. In 2003, another NAS report was released reiterating this point. In 2004, the RCDC was established to apply new technologies to this issue at the NIH. These technologies became mandatory through the NIH Reauthorization Act in 2006.

The RCDC is an electronic reporting system that reports NIH spending to Congress and the public, reaching across 27 ICs each fiscal year and reporting on approximately 360 research and disease areas. Dr. Hayes noted four key benefits of the system: (1) consistency (e.g., establish a consistent definition for each disease category across the NIH); (2) transparency (e.g., show the public exactly which projects fall into each category); (3) efficiency; and (4) opportunities for further portfolio analysis.

The RCDC process, because the NIH is developing a centralized database of all research, will allow the NIH to develop definitions and provide responses much more quickly. The biggest benefit will be having the database available for other types of analysis (e.g., compare the NIH portfolio with those from other agencies to determine where there are gaps in funded research projects).

In explaining how the RCDC works, Dr. Hayes stated that much of the information that now comes in through grants.gov in electronic form – title, abstract, specific aims, and public health relevance sections – is combined. The project description text is then run against an NIH-created thesaurus that has more than 300,000 multi-word concepts. A weighted list of concepts, or "fingerprint," of the research project is created, as is a category definition made up of all the concepts related to a disease. Every project funded by NIH is run against each disease category. If it sufficiently matches one, then the project is categorized in an automated fashion. If a project falls into multiple categories, it gets reported at 100 percent in each of the matching categories.

Dr. Hayes indicated that to craft the definitions for the disease categories, OPASI coordinates experts from across the NIH. In terms of future activities, the NIH plans to roll out information about the RCDC project. A set of crosswalk numbers for 2007 will be released to help explain the transition to the RCDC system.

Discussion

Dr. Katz expressed concern that members within the NIH, scientific communities, and the public may be confused if crosswalk numbers are used only in 2007. He commented that it may be worth utilizing the RCDC as a demonstration project for 2 years and then release numbers. Dr. Hayes reminded Council members that most NIH projects run 4 or 5 years, so there is only an overturn of projects at about 20-25 percent. He also noted that the longer the RCDC serves as a demonstration, the longer IC staff will have to duplicate efforts and cost to generate these numbers.

Dr. Hahn voiced concern that it could appear as though the agency is inflating what is being done with the dollars, particularly because these numbers cannot be compared against NIH's appropriation. Dr. Hayes indicated that he has met with House and Senate staff members, and has reminded them that the NIH has been triple or quadruple counting for 20 years; it is a standard process that requires frequent communication and explanation, because research is transdisciplinary in nature, there are overlaps between projects, overlaps between categories, etc.

Dr. Shulman, the first Director of NIAMS, agreed with Dr. Hahn and stressed the importance of considering what each individual NIH stakeholder community will think when they see numbers that could be construed as inflated.

Council member Dr. Betty Diamond, Chief of the Laboratory of Autoimmune Diseases at the Feinstein Institute of Medical Research and Professor at Albert Einstein College of Medicine, also expressed concern, as the system becomes more and more public and is made transparent, of how the numbers will be interpreted. The whole system inflates what goes into the NIH so enormously that it could be abused at a time when the NIH is hurting for funding. Anything that might be used to indicate that the NIH is getting more funds than it actually is receiving will require a very compelling educational program tied to it.

Dr. Katz noted that having the RCDC located centrally and using common definitions are critical. The RCDC will be used in many positive and helpful ways, but it also will be used egregiously. The program represents a key commitment to transparency, communication and consistency – both in terms of message and in terms of data. He reiterated his concern that there should be 2 years of overlap between the RCDC and the current system used at NIH.

Dr. Hayes noted that as part of the RCDC format, the NIH is required not only to implement the new categorization process, but also to provide a link between grants and publications. Even on the NIH web site, this will be a requirement in the near term. The DPCPSI has a subcommittee on resource development analysis looking at portfolio analysis more strategically. Dr. Katz again emphasized the critical importance of communication as this project is introduced. NIAMS Advisory Council member Ann Kunkel, Education Coordinator for Pediatric Rheumatology, University of Kansas Medical Center, noted that the RCDC may be difficult to communicate to voluntary organizations. It may be difficult for individuals who are not experts or highly educated to explain the RCDC numbers and approach Congress to ask for money for research. Dr. Hayes noted that many of the public liaison officers and communication directors at the NIH have been engaged to help establish the messages that need to be relayed, as well as to establish a broad communication plan.

Dr. James Weinstein, Professor and Chair of the Department of Orthopaedics at Dartmouth-Hitchcock Medical Center and a member of the Council, asked if other organizations within the federal government have a similar model and whether there are any examples where there are cross-institute funding that would apply to the RCDC scenario. Clear examples would be helpful in explaining the RCDC. Dr. Hayes indicated that it is hoped that the program includes vignettes that explain and provide examples. He noted that he has had discussions with the Veterans Administration (VA), the Centers for Disease Control and Prevention (CDC), and NASA, which are interested in types of information management technologies similar to RCDC.

VII. AN INTERIM REPORT FROM THE NIH WORKING GROUP ON WOMEN IN BIOMEDICAL CENTERS

Dr. Vivian Pinn, NIH Associate Director for Research on Women's Health, described a trans-NIH initiative, the NIH Working Group on Women in Biomedical Careers, which she Co-Chairs. Dr. Pinn drew Council members' attention to a report titled *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, which was sponsored by NIH's ORWH, Eli Lilly and Co., the National Science Foundation, the Ford Foundation, and the National Academies. The report was released approximately 1.5 years ago, and it indicated that much still needs to be done to support women in careers in science, including the fact that their achievement and sustained success is not related to a lack of innate ability or talent, but primarily related to unintentional biases and outmoded institutional structures. The report also called on academic institutions and funding agencies of the federal government to examine policies and regulations to ensure they are not furthering unintentional biases or negatively affecting the advancement of women.

NIH Director Dr. Elias Zerhouni responded to the report by appointing the NIH Working Group on Women in Biomedical Careers, which was given the following objectives: (1) consider recommendations from the National Academies report; (2) give attention to the NIH intramural community and the concerns of intramural women scientists; (3) consider the broader context of girls and women in science; and (4) provide special attention to issues of barriers, minority women scientists, and mentoring.

The Working Group includes 18 members, is Co-Chaired by Drs. Zerhouni and Pinn, and includes NIH Deputy Directors, IC Directors, a dual career couple, a postdoctoral fellow, intramural scientists, and extramural grants administrators. The Working Group has established a number of subcommittees to facilitate and expand interactions among others within the NIH, and a Web site has been created (accessible on the www.nih.gov main page). Dr. Pinn then described the activities of the following Working Group subcommittees:

- **Subcommittee 1: Development of a "Best Practices" conference/workshop.** Dr. Pinn reported that on March 4, 2008, the Women in Biomedical Research: Best Practices for Sustaining Career Success will be held at the NIH Natcher Conference Center. The conference will provide examples of systems approaches used by businesses, military and academic health centers, as well as the NIH to ensure sustained career success. The economic cost of loss of leadership, as well as the economic cost of providing infrastructure to sustain the careers of women and minorities will be addressed throughout the conference.

- **Subcommittees 2-5: Examination of extramural funding mechanisms and policies, including gender equity in NIH funding reviews and publication of demographics of funding applicants and recipients.** Information has been updated on sex/gender in the NIH extramural biomedical research community: (1) the number of RPGs per PI is higher for males, (2) the gap between male and female success rates on Type 2 (continuing) NIH R01 grants is narrowing; (3) the average female request for RPGs is less than the average male request; and (4) females and males both receive about the same percentage of their requests. In addition, there has been a review of federal policies associated with child care, parental

leave, extension of time, and availability of temporary replacement help to understand the benefits available under extramural grants. A list of frequently asked questions regarding the aforementioned policies has been posted on the Working Group web site and on the Office of Extramural Research (OER) web site.

- **Subcommittee 6: Expansion of support for research on the efficacy of programs to reduce gender bias.** This subcommittee is examining factors that may account for the paucity of women in science and engineering, as well as evidence about the effectiveness of programs to reduce bias. A Request for Applications (RFA) is under development, and the subcommittee is considering research on ways to train scientists who serve on tenure and recruitment committees to understand their potential for bias.

- **Subcommittee 7: Examination of NIH's role in enforcement of anti-discrimination laws.**

- **Subcommittee 8: Expansion and development of mentoring programs.** This subcommittee identified three major challenges related to the mentoring of scientists that may disproportionally affect women during their professional development:

    - The unavailability of trained mentors, including those familiar with issues that are frequently important to or disproportionately affect women.
    - The absence of avenues for networking among women scientists that are vital to providing information and support, as well as avoiding "feelings of isolation" and pitfalls.
    - The scarcity of structured training opportunities offering career development for scientists, including those that address issues of concern to women and/or issues that disproportionally affect women.

  A survey across the NIH found that there are a number of career development and mentoring programs in place both intramurally and extramurally. These findings have been summarized in a document that is available online at http://www.womeninscience.nih.gov/pdf/NIHPrograms.pdf. Next steps include reviewing and considering recommendations from the November 2007 meeting titled "National Leadership Workshop on Mentoring Women in Biomedical Careers." The workshop included more than 600 registrants and resulted in recommendations for institutions, for the NIH, and for both the NIH and institutions.

- **Subcommittees 9-10: Changing the NIH work culture to ensure the recruitment, retention, and advancement of women at the NIH.** This subcommittee is considering changes to the work culture at the NIH, and will work towards eliminating possible impediments to the recruitment, retention, and advancement of women scientists in the NIH intramural research program. Topics being considered include: (1) mentoring and the need for role models; (2) provision of necessary training for professional development; (3) change of the NIH work culture to enhance flexibilities; (4) enhanced availability of child/family care options; and (5) development of better recruitment strategies. Dr. Pinn noted that the NIH is planning to build a new child care center on Campus, and is establishing a trans-NIH

mentoring committee that will be responsible for mentor training and provision of mentoring for postdoctoral fellows.

- **Subcommittee 11: Ensuring the integration of women into bioengineering fields.** This subcommittee is considering issues concerning women in engineering/bioengineering. Topics being discussed include: (1) developing partnership outreach programs to encourage female student participation in engineering and the quantitative sciences; (2) expanding current NIH programs to include bioengineering and increasing the representation of women with bioengineering backgrounds and interests; and (3) producing an educational video to profile the bioengineering field and its role models. As a first goal, the subcommittee is working on increasing the visibility of engineering and women engineers at the NIH.

Dr. Pinn concluded her remarks by discussing the future directions of the NIH Working Group on Women in Biomedical Careers. These include: (1) determining legal and policy implications of suggested new programs; (2) considering recommendations from the Mentoring Leadership and the Best Practices Workshop; (3) taking findings, information, recommendations, and accomplishments out to the public in a series of meetings across the country; (4) encouraging all ICs to consider innovative programs and continuing the efforts of the Working Group; and (5) developing and implementing new career development and advancement initiatives in collaboration with the ICs, OAR, and OER.

Discussion

Dr. Sweeney asked if female grantees having fewer grants and the average size of grants being lower is tied to an age issue and whether the average male investigator is older than the average female investigator. Dr. Pinn indicated that existing data have not been looked at in this manner, but that data on the ORWH web site may provide more information regarding his questions. She suggested that this may be more related to the type of grant mechanism that is applied for (e.g., Center grants vs. R01s). Dr. Sweeney noted that at his institution, the average female faculty member is younger than the average male faculty member, and younger faculty tend to have fewer and smaller numbers of grants.

Council member Dr. Kathleen Green, the Joseph L. Mayberry Professor in the Department of Pathology/Cancer Center at Northwestern University Medical School, discussed the availability of child care and asked whether efforts to improve the child care situation – both intramurally and extramurally – could have an impact with incentives to get institutions more active in this area. She added that practical issues related to support of families are major barriers to women sustaining their careers. Dr. Pinn noted that NIH appropriated funds can be used in some instances to support child care, but institutional policy and how institutions manage funds from other sources are determining factors. Providing support and demonstrating models that are effective may help.

Dr. Diamond noted that the National Institute of Allergy and Infectious Diseases (NIAID) has started to award child care grants and asked whether there is any information on their success or lack thereof. Dr. Pinn indicated that these initiatives have not been in place long enough to determine their effectiveness. She added that issues related to child care and family support are

the most common issues they hear about from young women scientists. She asked Council members for any suggestions and input, and commented that NIAID's child care grants may help inform future activities.

VIII. THE PATIENT REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS): AN NIH ROADMAP INITIATIVE

Dr. Susana Serrate-Sztein, Director of NIAMS' Division of Skin and Rheumatic Diseases, and Lead Project Officer for PROMIS, described overarching themes of the NIH Roadmap, including: (1) new pathways to discovery; (2) research teams of the future; and (3) re-engineering the clinical research enterprise (i.e., implementing new paradigms in how clinical research information is collected, used, and reported; incorporating advances in information technology, psychometrics, and qualitative, cognitive, and health survey research; and developing new partnerships). She described the role of PROMIS in the clinical research enterprise, noting that patient reported outcomes provide important information regarding therapeutic effects. These patient reported outcomes separate efficacy from placebo in randomized trials (more effectively than some previously considered, physician-generated, "objective" measures). Dr. Serrate-Sztein explained that PROMIS represents a paradigm shift in assessing patient-reported outcomes. The associated item banks and computerized adaptive testing (CAT) system will be significant improvements over current assessment (e.g., paper-and-pencil vs. computer administered, classical vs. modern psychometric theory).

Dr. Serrate-Sztein noted that the advances anticipated by PROMIS are poised to transform clinical research through: (1) evaluation of therapeutic intervention in pain, fatigue, and physical functioning; (2) provision of up-to-date, relevant, and sensitive item banks; and (3) streamlined CAT tools linked to advanced data management and analysis systems that adapt to the individual setting. She described the roles of current PROMIS grantees at Northwestern University, the University of Washington, Stanford University, the University of North Carolina, the University of Pittsburgh, Stony Brook University, and Duke University. The NIH PROMIS team consists of NIH PROMIS Science Officers, as well as NIH representatives from almost all NIH ICs.

Dr. David Cella, Chair of the PROMIS Steering Committee, explained that PROMIS integrates the fields of information technology, psychometrics, qualitative research, and survey research. Enduring PROMIS values, as described by Dr. Cella, include: (1) scientific rigor (interaction of qualitative and quantitative methods, commitment to measurement excellence); (2) transparency (open access to concept definitions, bank development and validation process, item-level decisions, and bank-level decisions); and (3) flexibility for the researcher (item content, mode of administration).

Highlights from "PROMIS-1," the first 5 years of the Roadmap (we currently are in the middle of Year 4) are that there is a consensus-driven patient reported outcomes framework, qualitative research on more than 1,000 people, quantitative research on more than 20,000 people, and nine item banks that are available to collaborators (with several more in development). In addition, there is a web site and functioning assessment center, upcoming clinical validation studies in chronic disease populations, and a clear path and agenda for "PROMIS-2." Dr. Cella noted that

PROMIS is more than just the network projects and described independent projects, supplements, and sample spin-off projects related to the initiative.

Dr. Cella characterized an "item bank" as a large collection of items measuring a single domain (i.e., pain, fatigue, etc.) that form the basis for tailored/adaptive testing. Items in the same bank are linked on a common metric, and items are selected to maximize precision and retain clinical relevance. He noted that when the patient reported outcomes drive the sample size requirement, investigators should be able to lower sample size requirements overall, representing a major cost savings. In terms of PROMIS item bank development, work began with clear concept definitions and careful attention to terminology and definitions. A comprehensive review of existing approaches to measuring core concepts followed, as did the development of new and modified items. These items were classified and narrowed to the best available, which underwent readability analysis and revisions, as well as focus groups and cognitive interviews.

These efforts have allowed for the creation of short forms and CAT. Short forms developed from item banks select a set of items that are matched to the severity level of the target population. All scales built from the same item bank are linked on a common metric. Dr. Cella explained that CAT represents the administration of a survey by selecting questions based on a person's response to previously administered questions. By iteratively estimating a person's standing on the domain (e.g., depressive symptoms) and administering the most informative items, the desired level of precision can be obtained using the minimal possible number of questions.

Dr. Cella then provided an example of short forms and CAT – comparing results from respondents based on two different depressive symptoms from a total of 752 individuals who responded to the 28 items in the PROMIS depressive symptoms item bank. He demonstrated how PROMIS estimates a person's standing on a domain through an iterative process of estimating where that person is likely to be and then picking appropriate questions based on that estimation. Dr. Cella also illustrated how CAT assessments can achieve higher precision than fixed forms. In addition, Dr. Cella used fatigue as a further example, summarizing that calibrated item banks can be used to create a standard static instrument, construct short forms, enable CAT, and select items based on unique content interests and formulate custom short-form or full length instruments. He explained that in every case studied, using a validated, pre-calibrated item bank allows instruments to be pre-validated and produce standardized scores on the same scale.

Dr. Cella noted that the PROMIS Assessment Center enables administration of PROMIS item banks for clinical research, population surveillance, and clinical practice. Through the Assessment Center, there is an accessible item library through which users can generate CAT and select a patient reported outcome. The Assessment Center also includes capabilities for study setup, maintenance, and administration. In the summer of 2008, there is a planned release of a new version of the Assessment Center with enhanced capabilities (e.g., building a patient reported outcome, item customization in an instrument, advanced study setup, dynamic selection of participant registration fields, and advanced searching.) Activities anticipated in 2008-2009 include finalizing calibrations and CAT; conducting clinical validation studies, feasibility tests, and user group meetings; and forging sustaining partnerships.

Discussion

Dr. Weinstein asked about public-private partnerships and instrument ownership issues. Dr. Cella indicated that the process involves eliminating clear intellectual property concerns early; as a result, there were a number of questions and questionnaires that were not considered based on copyright holders' expectations. He indicated that about 90 percent of the instruments are free of intellectual property concerns. Dr. Paul Plotz, NIAMS' Acting Deputy Director, asked about culture and language specificity associated with the project. Dr. Cella indicated that the PROMIS team has a sense of how culture- and language-specific the system is. There is a translation team examining the linguistic aspects, and efforts have been made to make the language of the questions easily translatable. He added that it is possible to determine whether the response to a specific question is different based on cultural variability using a technique known as differential item function.

Dr. Weinstein asked about the implementation strategy, noting that he and his colleagues have found it difficult for patients to interface with some of these instruments. Dr. Cella indicated that researchers at the University of Washington are working on the interface and will incorporate compliance recommendations to increase user friendliness.

Dr. Hahn asked if a user could visit the PROMIS web site and use the CAT for fatigue in a study at this point. Dr. Cella indicated that it is possible to see this information; however, users currently have to agree to terms and conditions, one of which is that there are no longitudinal clinical validation data yet. Therefore, anyone using the banks must share a report with the PROMIS team indicating how the banks perform. The software is currently designed for a single assessment but the capability for longitudinal evaluations will be added in the summer of 2008.

Dr. Serrate-Sztein indicated that all funded NIH Roadmap projects undergo a mid-course review. The mid-course review for PROMIS has been posted online. A concept has been presented to continue PROMIS beyond its initial 5 years – this concept has been approved. Anticipated activities include testing PROMIS in a large clinical trial and ensuring that the resources are available to researchers and the public. Dr. Katz clarified that all current Roadmap activities, including PROMIS, will be assessed against potential new Roadmap initiatives as priorities are set.

IX. OSTEOARTHRITIS INITIATIVE UPDATE

Dr. Gayle Lester, Project Officer for the Osteoarthritis Initiative (OAI), reminded the Council that the goal of the Initiative is to create research resources to aid in the identification and evaluation of biomarkers as candidates for surrogate endpoints for OA. The project includes development of a prospective, natural history cohort to be followed for 5 years. Materials to be collected include clinical and imaging data, as well as biological specimens. The OAI includes a large, multi-center prospective cohort study of knee OA that enrolls subjects with a broad spectrum of knee disease. The project is intended to evaluate biomarkers/risk factors for both onset and progression of knee disease with adequate statistical power for incident symptomatic knee OA.

The OAI is a public-private partnership, with intellectual input and planning (including input from private industry, academic investigators, government agencies, and private foundations), as well as financial input from private industry and government. Dr. Lester noted that the OAI Data Coordinating Center is at the University of California, San Francisco. Clinical Centers are at the Ohio State University, University of Maryland School of Medicine, University of Pittsburgh, and Memorial Hospital (Rhode Island). After providing an overview of the OAI cohort design, Dr. Lester described eligibility criteria (e.g., risk factors such as overweight, aged 70-79, history of knee injury causing difficulty walking for at least 1 week, history of knee surgery, etc.). Clinical variables assessed include knee symptoms, activity, limits, pain severity; patient global assessment; walking ability and endurance; etc. Biological specimens collected include blood and urine.

There is also an imaging component to the OAI – many experts feel that biomarkers for knee OA will be found in imaging as opposed to biochemical surrogates. Subjects receive MRI exams of both knees, fixed flexion posteroanterior (PA) x-rays, and in some cases fluoro-guided knee x-rays.

Dr. Lester reported that baseline enrollment has been completed (4,794 subjects have been enrolled). The 12-month followup visits are 100 percent completed at a 92 percent retention rate. The 24-month visits are 93 percent complete, at an estimated retention of more than 90 percent. The 36-month visits are 50 percent complete; 48-month visits will begin in March 2008 and end 2 years later.

Dr. Lester described the OAI subcohort characteristics. The progression subcohort (patients with knee osteoarthritis at baseline) represents 29 percent of total enrollees; the incidence subcohort (those at elevated risk or who developed knee OA during the study) includes 68 percent, while the control subcohort includes 3 percent of enrollees. The overall study population is roughly 60 percent female and approximately 21 percent of enrollees belong to a minority group. History of knee injury is a high risk factor, particularly in men but also in women, and Dr. Lester commented that the development of OA in knees that have been injured is striking (49% of men and 35% of women in the incidence subcohort). Dr. Lester then described public data releases to date, noting that data are available online to investigators and interested parties.

The OAI Web site has been active since June 29, 2006; as of December 1, 2007, there were 744 registered OAI online users from 40 countries (528 users from the United States, and 216 international users). A total of 117 researchers have downloaded datasets as of December 1, 2007. Recently, the Osteoarthritis Research Society International held a data users workshop that included more than 200 participants to learn how to use the web site and the data. Dr. Lester noted that the scientific community has embraced the OAI and there have been many applications for R01 projects related to these efforts (e.g., projects using OAI data to test hypotheses, adding components such as bone mineral density to the study, etc.).

Discussion

Dr. Weinstein asked about how Institutional Review Board (IRB) and other issues are addressed when data are transferred to other centers, particularly in terms of informed consent. Dr. Lester

indicated that all of the data are de-identified at the clinical centers and given a study ID that is held only at the clinical center. The data then are transferred to the coordinating center, which further de-identifies the data before posting the information on the Internet. Patients are consented for public release of the data in advance; IRB approval is obtained before patients are brought to the clinic.

Dr. Katz informed the Council that to date, the OAI is a $60 million endeavor, with approximately 33 percent of funding coming from the pharmaceutical industry (the remaining two-thirds is funded from across the NIH). Dr. Jacobs asked about imaging and the fixed-flexion view; Dr. Lester replied that this is a standing, weight-bearing view. She added that when negotiating with imaging companies, magnets were purchased for each of the four centers at a cost savings relative to what it would have cost for patients to have these images taken at a radiologist's office. This also has increased the accessibility of these tests.

Dr. Klippel noted that he and his colleagues are interested in developing a risk assessment tool. The OAI cohort will help in this regard. He asked to what extent a small number of controls will be limiting. Dr. Lester explained that many of the incidence cohort subjects are completely normal and simply have potential risk factors, but no x-ray evidence of knee OA. It is possible that these individuals can be used as controls even though they have a risk. The control group is a small number of subjects who have no risk factors with regard to obesity or knee injury and additionally have no signs of radiologic OA in any joint.

Dr. Cliff Rosen asked about future activities, given that large amounts of data will be coming in. He asked what is envisioned beyond 2010 outside of independent R01 projects and what industry's response has been. Dr. Lester noted that it is hoped to encourage more grants for data analysis. There are funds available within the contract for some limited analyses; the particular hypothesis that has been posed in the contracts was whether MRI is a more sensitive tool for seeing change in joint space than x-ray. This will be a very limited analysis. With regard to industry, all industry partners have all of the data, including the images. Dr. Lester indicated that industry has been somewhat disappointed in that the 1-year data show MRI changes that were less than anticipated. Dr. Katz indicated that more years' worth of data will help; Dr. Lester noted that the analysis from the 2-year visit will be released in approximately 1 month, and that industry members serve on the OAI Advisory Committee.

X. NIAMS FY 2009 INITIATIVES

Dr. William Sharrock of NIAMS' Division of Musculoskeletal Diseases explained that there have been impressive recent reports of successful genome-wide association analyses; in the near future, there will be areas of the NIAMS mission for which these efforts will be extremely useful. The Institute currently is trying to assess the needs of the various communities with which it interacts in making use of this important new tool. A roundtable meeting is planned for next month with representatives from mission areas from across the NIAMS interests. The purpose is to obtain input on what challenges are associated with making use of genome-wide association approaches and to begin more deliberately and systematically assessing the directions in which the Institute might proceed.

A few Council meetings ago, Dr. Sharrock suggested that the Institute create an initiative that would invite investigators to apply for support in order to conduct analyses of existing datasets and encourage sharing of data. Specifically, support would be offered to help experts who are in a position to replicate initial findings. One of the lessons of genome-wide association studies learned to date is that not much is learned in most cases from initial genome-wide scans. Hundreds, sometimes thousands of signals are found, sometimes at minimal statistical significance; they are mostly false positives and the only critical test of which are true signals is to test them again in a new population.

Dr. Sharrock explained that the idea would be to advertise that the NIAMS is interested in supporting groups that may have conducted a first analysis or may have access to data from collaborators where there has been a report or there are preliminary data indicating that there are informative associations in a particular disease area. This critical test would be carried out with a more limited set of polymorphisms in a different population. Applicants would be those who have access to well-characterized clinical cohorts that would be useful for this purpose and need support now not just for analysis, but for genotyping a new population. This will require more substantial resources, although the cost of the effort would vary based on the number of polymorphisms necessary. Dr. Katz noted that there will be a workshop Co-Chaired by Drs. Rosen and Sharrock to further explore this concept.

Discussion

Dr. Hahn noted that this activity is badly needed and asked how the Institute plans to limit these endeavors. Dr. Sharrock explained that the constrained competition (and constrained funding) would serve to limit this work. A single competition each year for several years is planned with a committee that hopefully would retain the same expert reviewers from year to year. Within the Institute, it also will be important to monitor this project for redundancy. Dr. Hahn then asked if this competition would be kept to North American populations, or whether other ethnic groups such as those in Asia would be considered. Dr. Sharrock indicated that it may be possible for a domestic institution to partner with foreign collaborators. Many useful cohorts exist outside of North America, and every care would be taken to construct this initiative so that the Institute can benefit from those cohorts in these types of studies. Dr. Rosen noted that a number of U.S. investigators have collaborated with foreign investigators who have these types of cohorts. He characterized this as a very exciting opportunity for work that is badly needed in complex diseases such as osteoarthritis.

Dr. Betty Diamond commented that this initiative could provide the opportunity to ensure that the DNA collections are coordinated with good clinical data sets. A coordinated effort is needed to make sure this coordination is done through a shared activity in determining what is going to be captured.

XI. PORTFOLIO – OVERVIEW OF THE ORTHOPAEDICS PROGRAM

Dr. James Panagis presented this overview in closed session.

XII. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 576 applications in closed session requesting $126,073,786 and recommended 576 for $125,741,783.

XIII. ADJOURNMENT

The 64th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 4:00 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.

Madeline Turkeltaub, C.R.N.P., Ph.D.
Executive Secretary, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council

Director, Division of Extramural Research Activities, National Institute of Arthritis and Musculoskeletal and Skin Diseases

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Chairman, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council

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