



National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

September 26, 2006

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

MINUTES OF THE 60th MEETING

**September 26, 2006
8:30 a.m. to 4:00 p.m.**

I. CALL TO ORDER

The 60th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on September 26, 2006, 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:

Dr. Kevin Campbell
Dr. Gena R. Carter
Ms. Carmen Cheveres DeMummy
Dr. Lee Green
Dr. Bevra H. Hahn
Dr. Joshua Jacobs
Dr. Brian L. Kotzin
Dr. Martin J. Kushmerick
Dr. Jack E. Parr
Dr. Lawrence G. Raisz
Dr. Randy N. Rosier
Dr. Raymond Scalettar
Dr. John R. Stanley

Council members not present:

Dr. Graciela S. Alarcon
Ms. Patricia McCabe
Dr. Robert J. Oglesby (Ex Officio)
Dr. Steven L. Teitelbaum
Ms. Sharon F. Terry
Dr. Jouni J. Uitto

Staff and Guests:

The following NIAMS staff and guests attended:

Staff

Dr. Janet Austin
Dr. Carl Baker
Dr. Michael Bloom
Mr. Gahan Breithaupt
Dr. Eric Brown
Dr. Amanda Boyce
Ms. Kelli Carrington
Mr. Richard Clark
Ms. Anne Connors
Ms. Teresa Do
Mr. Erik Edgerton
Ms. Sharon Fair
Mr. Raymond Fleming
Ms. Valerie Green
Dr. Elizabeth Gretz
Dr. Steven Hausman
Ms. Jane Hymiller
Dr. Daniel Kastner
Dr. Stephen Katz
Ms. Juliana King
Dr. Helen Lin
Ms. Anita Linde
Dr. Kan Ma
Dr. Joan McGowan
Ms. Leslie McIntire
Mr. Robert Miranda-Acevedo
Ms. Melinda Nelson
Dr. Glen Nuckolls
Dr. John O'Shea
Dr. James Panagis
Ms. Karin Rudolph
Dr. Susana Serrate-Sztein
Dr. William Sharrock
Ms. Sheila Simmons
Ms. Helen Simon
Ms. Robyn Strachan
Mr. Yen Thach
Mr. Michael Toland
Dr. Madeline Turkeltaub
Dr. Bernadette Tyree

Dr. Fei Wang
Dr. Ping Wang
Dr. Yan Wang
Dr. Chuck Washabaugh

Guests

Ms. Nahid Akhyani, Office of the Director, NIH
Dr. Ronald Barnett, Social and Scientific Systems, Inc.
Ms. Patti Brandt-Hansberger, Office of Legislative Policy and Analysis, NIH
Dr. Jonelle Drugan, National Heart, Lung, and Blood Institute, NIH
Ms. Ann Elderkin, American Society for Bone and Mineral Research
Ms. Christy Gilmour, American Academy of Orthopaedic Surgeons
Ms. Darlene Kerr, Circle Solutions
Dr. Michael Martin, Center for Scientific Review, NIH
Ms. Becky Minnillo, Society for Investigative Dermatology
Dr. Alan N. Moshell
Ms. Roxanne Yaghubi, Society for Investigative Dermatology

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept the minutes of the 59th Council meeting, held on May 23, 2006.

III. FUTURE COUNCIL DATES

Future Council meetings are currently planned for the following dates:

February 27, 2007
June 12, 2007
September 27, 2007
January 29, 2008
May 27, 2008
September 23, 2008

Dr. Katz alerted Council members to the fact that the May 27, 2008, date is the Tuesday following Memorial Day Weekend. Therefore, an alternate date in late May or early June is being considered.

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz began his report by inviting Council members to review the NIAMS Shorttakes online, which go into more detail on many of the topics covered in this Director's Report. He also thanked the following outgoing Council members whose terms ended with this meeting: Dr. Graciela Alarcón, Dr. Randy Rosier, Dr. John Stanley, Dr. Steven Teitelbaum, and Ms. Sharon

Terry. Dr. Katz thanked these outgoing Council members for their input and extraordinary level of commitment and expertise to NIAMS.

Personnel Changes

At the Institute level, Dr. Carl Baker has been named as the new Program Director for Skin Biology and Diseases in the NIAMS Extramural Program (EP). Dr. Baker previously served as Chief of the Cellular Regulation and Transformation Section, Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute (NCI). Dr. Fei Wang has rejoined NIAMS as the Program Director for Musculoskeletal Development, Tissue Reengineering, and Regenerative Medicine in the Musculoskeletal Diseases Branch of the NIAMS EP. Dr. Wang first worked at NIAMS in 2003 as the Program Director for Muscle Biophysics and Cell Biology. Before returning to the Institute, she worked for 2 years at the National Institute of Biomedical Imaging and Bioengineering. Dr. Amanda Boyce, previously of the NIAMS Intramural Research Program's (IRP) Cartilage Biology and Orthopaedics Branch, is the new Program Director for Muscle Development and Physiology in the NIAMS EP.

Dr. Kan Ma has joined the NIAMS Extramural Program Review Branch as a Scientific Review Administrator. Before coming to the Institute, Dr. Ma was the Director of the Analytical Instrumentation Laboratory at the Institute of Chemical Biology and Drug Discovery at Stony Brook University. Dr. Chuck Washabaugh also joined the Institute as a Scientific Review Administrator in the Extramural Program Review Branch. Prior to coming to NIAMS, Dr. Washabaugh served as a Research Assistant Professor in the Department of Cell Biology and Physiology at the University of Pittsburgh School of Medicine. Sharon Fair is a new Extramural Program Administrative Assistant, coming to NIAMS from the Intramural Program of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

At the NIH level, in August of this year, President Bush appointed Dr. John Niederhuber as the 13th Director of the NCI. Dr. Niederhuber has served as the Acting Director of NCI since Dr. Andrew von Eschenbach stepped down in June to serve as Acting Commissioner of the U.S. Food and Drug Administration (FDA). Searches for the positions of National Center for Research Resources (NCRR) Director and NIDDK Director are ongoing.

Update on Budget and Congressional Activity

On June 13, 2006, the House Appropriations Committee completed its markup of the Fiscal Year (FY) 2007 appropriations bill for the Departments of Labor, Health and Human Services, Education, and related agencies. The House bill includes \$28.3 billion for the NIH, the same as the FY 2007 President's budget when adjusted for the global AIDS transfer. The amount proposed for NIAMS is \$504.5 million, a decrease of approximately \$3.4 million below the comparable FY 2006 level and the same as the President's budget request. Most Institute/Center (IC) budgets were reduced to allow for increases to the NIH Office of the Director for Biodefense Countermeasures, the Director's Discretionary Fund, the establishment of the Office of Portfolio Analysis and Strategic Initiatives (OPASI), and to the NCRR for Clinical and Translational Science Awards and extramural facilities construction.

The Senate Committee on Appropriations marked up the bill on July 20, 2006. The Senate mark provides \$28.5 billion for NIH, an increase of approximately \$200 million over the President's budget request and the House level. The Senate bill included \$508.6 million for NIAMS, representing an increase of \$1 million over FY 2006 and \$4 million more than the President's budget request and the House allowance. House and Senate conferees must now reconcile the differences in the two bills before the final appropriations bill can be passed. If this does not occur prior to October 1, 2006, the NIH will begin the fiscal year with a continuing resolution.

Highlights of Recent Scientific Advances

- In a study published in the *New England Journal of Medicine*, researchers led by Raphaela Goldbach-Mansky in the NIAMS IRP found that a drug called anakinra brings marked improvement in both symptoms and inflammation underlying neonatal onset multisystem inflammatory disease (NOMID). NOMID is a rare and debilitating disorder that affects numerous organs and body systems.
- In collaboration with researchers at the National Institute of Child Health and Human Development, Dr. Juan Rivera, Director of the NIAMS Office of Science and Technology and Chief of the Molecular Inflammation Section, led research demonstrating an immune system connection to Smith-Lemli-Optiz syndrome, a rare disorder of severe bone malformation, food intolerance, and susceptibility to infection caused by a genetic defect in cholesterol metabolism. Children with this syndrome have extremely low blood levels of cholesterol and high levels of a precursor of cholesterol, 7-dehydrocholesterol. Until this work, the mechanism of cholesterol's involvement in this syndrome had not been clear. This work offers new insight into that mechanism and provides clues that could change and improve the way that certain manifestations of the syndrome are treated. This research demonstrates for the first time that there is an immune function dysregulation in this syndrome. Traditionally, children with Smith-Lemli-Optiz syndrome have been treated with high-cholesterol diets and supplements to increase blood levels of cholesterol. In light of these findings however, a more appropriate therapy might be one that reduces dehydrocholesterol that accumulates on inflammatory cell membranes, causing them to overreact.
- Dr. Vittorio Sartorelli, of the NIAMS Muscle Gene Expression Group, Laboratory of Muscle Biology, in collaboration with colleagues in Italy and San Diego has shown that pharmacological interventions with deacetylase inhibitors can increase myofiber size and counter the functional decline of dystrophic muscles. The investigators increased the size of myofibers in dystrophin-deficient and alpha-sarcoglycan-deficient mice by inducing the expression of the myostatin antagonist follistatin in satellite cells. This work, published online in *Nature Medicine*, may provide a rationale for using deacetylase inhibitors in the pharmacological therapy of muscular dystrophies.
- In a study of rheumatoid arthritis, Dr. Joseph Holoshitz at the University of Michigan and colleagues studied 11 pairs of disease-discordant identical twins. Microarray studies were used to examine the expression of more than 20,000 genes and led to the detection of expression differences in 827 genes. Three genes were found to be markedly overexpressed

in patients with rheumatoid arthritis—none of these genes was previously known to be present in inflamed joints.

- A group of researchers led by Dr. Chandra Mohan at the University of Texas Southwestern Medical Center identified a gene in mice that may hold the key to the development and potential treatment of systemic lupus erythematosus in humans. In a study published in *Science*, this group demonstrated that the censoring of autoreactive B cells is impaired due to an alternative form of the gene *Ly108*. This gene is part of a gene family that has been linked to lupus-like disease in mice. Although the role of the alternative form of the gene has been shown only in mice thus far, the finding may have implications for human lupus.
- Two independent, NIAMS-funded studies have reported that mechanical stress can affect osteoarthritis biomarker release. Dr. David Eyre and colleagues at the University of Washington found differences in cartilage and bone-related biomarker release in different kinds of collegiate athletes (rowers, runners, and swimmers). In testing the effects of mechanical stress on cartilage from pigs, Dr. Farshid Guilak and associates at Duke University found that cartilage undergoing greater magnitudes of mechanical stress released increased levels of osteoarthritis-related biomarkers.
- A series of studies led by Dr. Harry Deitz of Johns Hopkins University School of Medicine and former NIAMS Council member Dr. Francesco Ramirez of the Robert Wood Johnson Foundation found that in mice, the popular anihypertensive medication losartin prevents aortic rupture, a deadly complication of the connective tissue disorder Marfan syndrome. Caused by a mutation in the gene that encodes for fibrillin-1, Marfan syndrome can affect the bones, eyes, skin, heart and blood vessels, nervous system, and lungs. Traditionally, scientists believed that fibrillin-1 played mostly a structural role in connective tissue disease. These researchers found that TGF- β is critically important in the pathophysiology of this disease. Studies in mice engineered to make low amounts of fibrillin-1 that had lung damage similar to that associated with Marfan syndrome demonstrated that administration of antibodies that bound TGF- β prevented lung and heart valve abnormalities. Losartin, an angiotensin-converting enzyme inhibitor drug currently on the market, demonstrates a similar effect to the antibodies. Researchers administered the drug to mice already experiencing changes to their aortas. After 6 months, the aortas of the Marfan-affected mice were indistinguishable from those of healthy mice—losartin not only stopped further damage, but had reversed damage that had already occurred.
- NIAMS grantee Dr. Frederick Kaplan, of the University of Pennsylvania, and colleagues discovered disease-causing mutations in a gene called *ACVR1* on the long arm of human chromosome 2 that lead to fibrodysplasia ossificans progressiva. In patients with this rare genetic disease, muscles, tendons, ligaments, and other connective tissues undergo a metamorphosis to bone. *ACVR1* encodes a protein called activin receptor type 1A, a bone morphogenetic protein that controls the formation of cartilage and bone. This work is reported in *Nature Genetics*.
- A study headed by Dr. Richard Spritz and colleagues at the University of Colorado Health Sciences Center found that patients with vitiligo—a pigmentation disorder in which white

patches of skin appear on different parts of the body—are predisposed to serious autoimmune diseases, such as rheumatoid arthritis, lupus, thyroid disease, adult onset insulin-dependent diabetes mellitus, pernicious anemia, and Addison’s disease. The study, funded in part by NIAMS, also confirmed a previously established link between sporadic vitiligo and autoimmune thyroid disease, pernicious anemia, Addison’s disease, and lupus.

- Another study funded in part by NIAMS and led by Dr. James T. Elder of the University of Michigan identified a gene called PSORS1, found in the major histocompatibility complex, that plays a role in determining who develops psoriasis. The researchers found that the allele HLA-Cw6, with a certain spelling in its code, may render individuals susceptible to the skin disorder.

Recent NIAMS Activities and Plans for the Future

The Osteoarthritis Initiative (OAI), a public-private partnership between the NIH and private industry that seeks to improve the diagnosis and monitoring of osteoarthritis as well as foster the developments of new treatments, has released its first set of data. The OAI was discussed at a previous Council meeting, and interest in utilizing data from this partnership is very high. Dr. Katz noted that the data are very robust, and will become even more so as longitudinal data become available. The OAI includes an enrollment of almost 5,000 people at risk of developing knee osteoarthritis, in the early stage of the disease, or with more advanced knee osteoarthritis. It is hoped that this initiative will provide breakthroughs in biomarker development and better understanding of osteoarthritis pathophysiology.

Programs and Activities at the NIH Level

Dr. Katz described the next generation of the NIH Roadmap for Medical Research. The NIH established a new office—the Office of Portfolio Analysis and Strategic Initiative (OPASI)—and began a three-phased process to identify ideas for a new set of Roadmap initiatives. In the first phase, consultation meetings were held in July and September of 2006. In the second phase, IC Directors and Office of the Director Program Directors submitted proposals for potential NIH Roadmap projects. NIAMS submitted five proposals in the areas of: (1) tissue engineering and regenerative medicine; (2) new and emerging imaging tools to assess bone strength for prediction of fractures and as surrogates for clinical trials; (3) standardized phenotype information management systems; (4) pharmacological, nutritional and exercise interventions for muscle wasting disorders; and (5) predictive and preventive approaches to autoimmune diseases. These five proposals, as well as other ideas from across the NIH and from the consultation meetings, will be pooled and posted for public comment in the third phase. This final phase will solicit input and additional ideas from the broad science and lay communities using a Web-based request for information. Following this three-phased approach, IC Directors will discuss the proposals and a Council of Councils will be formed to discuss and prioritize the proposals.

Dr. Katz also discussed the Patient Reported Outcome Measurement Information System (PROMIS) initiative. PROMIS relates to measuring patient-reported outcomes and is critical for evaluating new therapies. NIH leadership recently was provided with an update on this project, which has been ongoing for approximately 2 years. The initiative involves a multidisciplinary

collaboration of experts trying to identify a common language for distinguishing pain, fatigue, quality of life, and other subjective measures. A Spanish component of PROMIS has been translated and validated. Drug companies and the FDA have shown great interest in PROMIS.

The NIH Director's Retreat was held recently, and featured many topics of discussion that are of common interest across the ICs. The core theme of the Retreat was adaptive NIH strategies in the context of changing science and public health. NIH Director Dr. Elias Zerhouni introduced the Retreat by asking whether the NIH should stay the course, make drastic changes, or take other issues into consideration in terms of each topic discussed during the meeting. One major issue was review, particularly within the context of a time when the budget increases are not as robust as they have been in the past. Dr. Tony Scarpa, Director of the NIH Center for Scientific Review (CSR), presented his ideas for reshaping the review and application process (Dr. Scarpa discussed this at a previous NIAMS Advisory Council meeting). Dr. Zerhouni plans to appoint a group of IC Directors to formulate a plan with outside input to change the review process.

Also discussed at the NIH Directors Retreat was NIH's commitment to new investigators. Dr. Katz asked Council members for their thoughts on what the correct percentage of new investigators should be for the Institute, noting that in 2000, 18.6 percent of all R01s supported by NIAMS involved new investigators. In 2005, that percentage was 18.7 percent. About 30 percent of all new R01 awards (Type 1) funded by the institute have new investigators as the Principal Investigator (PI). Dr. Katz noted that these figures do not represent success rates, only the percentage of R01s going to new investigators.

Discussion

Council member Dr. Ray Scalettar, Clinical Professor of Medicine at George Washington University, asked about lobbying efforts related to the NIH budget and the prospects of the Senate bill being passed rather than the House bill. Dr. Katz responded by noting that the Institute does no lobbying—NIH leadership can explain the consequences of budget decisions if asked, and can describe future initiatives and current funded research. NIH representatives also can explain current scientific opportunities, gaps in knowledge, and research needs, and can explain the consequences on this work based on the budget NIH receives.

Council member Dr. Joshua Jacobs, of Rush University Medical Center, asked Dr. Katz to comment on the NIH Reauthorization Bill that is being considered on Capitol Hill. Dr. Katz explained that it has passed committee and is going to the floor of the House and that at present, there is no adjacent bill in the Senate.

Dr. John Stanley, Milton B. Hartzell Professor and Chairman in the Department of Dermatology at the University of Pennsylvania School of Medicine and a NIAMS Advisory Council member, applauded Dr. Katz for emphasizing how the study of rare diseases can lead to new discoveries that impact other diseases. He noted that the significance of how good science on rare diseases impacts more common human diseases cannot be predicted. Dr. Katz added that facilitating these types of discoveries is one of the most rewarding and exciting roles scientific research administrators play.

Dr. Scalettar noted that it is important to disseminate the recent findings by Drs. Dietz and Ramirez on Marfan syndrome. The current approach to treating these patients usually involves beta blockers, but these individuals may be better served by administration of an angiotensin II receptor blocker such as losartin. Dr. Katz added that the NHLBI is embarking on a study using losartin in patients with Marfan syndrome who have the abnormal gene. The challenge is in conducting a true case-controlled study in this context.

V. REVIEW OUTCOMES FOR R01 HUMAN SUBJECTS RESEARCH AT CSR

Dr. Michael Martin, Director of the Division of Physiology and Pathology at the NIH CSR, coordinates and monitors the initial peer review of grant applications submitted to NIH in the areas of cardiovascular disease; digestive disease; hematology; integrative functional and cognitive neurosciences; and musculoskeletal, oral, skin, urological and respiratory sciences. In providing his review of outcomes for R01 human subjects research at CSR, Dr. Martin noted that his comments exclude human subjects research or clinical research that is reviewed within the Institutes (e.g., multi-site clinical trials, Program Projects, Center Grants, etc.). The R01 pool is an appropriate and convenient mechanism to use in reviewing this topic because the NIH has implemented a system of percentiling that allows NIH Councils to interdigitate information across dozens of study sections to make informed decisions—the R01s reviewed at CSR are the only grants that are universally percentiled to allow for cross-study comparison. There has been a long-standing debate within the research community about how clinical research fares in peer review at CSR.

Various issues may affect peer review outcomes, including the impacts of: (1) human subjects concerns; (2) using human subjects versus not using human subjects and new versus established PIs; and (3) the rate of submission of the different types of applications (e.g., Type 2 versus Type 1, revised versus non-revised applications). For purposes of his presentation, Dr. Martin defined human subjects as living individuals about whom an investigator conducting research obtains data through intervention or interaction with the individual, or identifiable private information. In his analysis, applications reviewed by CSR and designated as Exemption 4 (primarily pathology archives, specimen banks, and/or data repositories) were not considered to include human subjects research. New investigators were defined as follows: the PI has not previously served as such on any U.S. Public Health Service-supported research project other than a small grant (R03), an Academic Research Enhancement Award (R15), an exploratory/developmental grant (R21), or mentored career development awards for persons at the beginning of their research career (K01, K08, K22, K23, and K25).

In reviewing data from 12 NIH Council rounds from October 2000 through May 2004 (a total of more than 30,000 R01 applications), Dr. Martin found that approximately 85 percent did not have human subjects concerns. He noted that not all human subjects concerns are equal in the minds of the reviewers—there is a cohort of applications that have human subjects concerns and receive good scores.

Dr. Martin explained that 17.56 percent of human subjects applications in his analysis scored in the top 20th percentile, which historically has been an important benchmark for funding at NIH. Of those applications that were not clinical (i.e., did not involve human subjects), 22.07 percent

fell in the top 20th percentile, highlighting the fact that there is a clear difference in peer review outcomes at CSR. Dr. Martin presented a chart plotting the outcome for each individual application over 12 Council rounds, comparing human subjects versus non-human subjects applications, new versus established investigators, and the impact of revisions on peer review outcomes. A number of differences were discussed. For example, new investigator Type 1 applications do not fare as well as established investigator Type 1 applications. Dr. Martin commented that NIH reviewers are required to take human subjects concerns into consideration when they vote their score, and they clearly do so. Roughly half of the difference in peer review outcomes between human subjects research and non-human subjects research can be accounted for by human subjects concerns.

Dr. Martin further explained that there are no differences between the rate of funded human subjects and non-human subjects applications within the new investigator Type 1, experienced investigator Type 1, and experienced investigator Type 2 of A1 applications. Differences across these groups of A1 applications remain, but these differences are not as great as those found in the initial applications. Interestingly, human subjects applications across these three groups improve dramatically on resubmission.

In terms of the impact on the rate of Type 2 application submissions and other activities, Dr. Martin explained that on a percent basis, human subjects PIs are less likely to reapply. Moreover, funded Type 1 new human subjects PIs who do not submit a Type 2 application are less likely to submit for another grant than are funded non-human subjects PIs. In addition to the fact that clinical investigators tend to not submit human subjects applications, the NIH is losing funded clinical researchers conducting human subjects research at a higher rate than the non-human subjects research clinical investigators. Despite all of the efforts made to get human subjects researchers into the system, they tend to move out of NIH-funded research after their grant concludes. Why are these PIs from funded human subjects applications more likely to stop applying for NIH-funded research after their initial R01 award than funded PIs from non-human subjects applicants? Are they dropping out of research entirely, or just out of NIH-funded research? Dr. Martin commented that these individuals may be serving as co-PIs on grants, and therefore would not be picked up by the system; or, they could have moved over to conducting industry-funded research. There is no method of determining this at present.

Dr. Martin summarized by stating that almost all of the difference in the peer review outcomes in CSR for this cohort of applications can be accounted for by two factors: (1) poor outcomes on human subjects concerns, and (2) a difference in the rate at which the various subgroups are applying for applications. To help get this important message out to the community, CSR will have a publication on this topic disseminated in the near future. Dr. Martin concluded by offering the following questions for future consideration:

- What can NIH do to improve applicant response to human subjects requirements?
- Why are Type 2 human subjects clinical PI submission rates so low compared with the non-clinical, non-human subjects applications?

- Why are funded new human subjects PIs not reapplying for grants at the same rate as funded non-human subjects PIs?
- What is the impact on the human subject research enterprise at NIH and what can be done about it?

Discussion

Council member Dr. Brian Kotzin, Vice President of Global Clinical Development at Amgen, asked if there are any differences in the outcomes from study sections that consider both types of applications versus study sections that consider only human subjects applications. Dr. Martin noted that an article appearing in the *New England Journal of Medicine* 2 years ago examined this issue and found no differences. In response to a question from Dr. Lawrence Raisz, a Council member and Director of the University of Connecticut Center for Osteoporosis, Dr. Martin indicated that the number of human subjects concerns declines on subsequent revisions of human subject applications.

In response to a question about success rates, Dr. Martin noted that his analysis included peer review outcomes but not success rates. Dr. Stanley asked if the analysis included a breakdown of whether PIs held M.D. or Ph.D. degrees. Dr. Martin indicated that this analysis did not have that information; however, Dr. Martin was able to determine that those PIs who held M.D./Ph.D. degrees were more likely to apply for a Type 2 R01 or to submit for another Type 1 R01 than were PIs without an M.D./PhD. degree.

Dr. Raisz commented that studies involving an intervention are much more likely to have human subjects concerns than epidemiological and other studies. Dr. Martin agreed, adding that although there currently is no way to analyze this, the NIH is developing a knowledge management tool that will allow for this type of study. Dr. Bevra Hahn, a Council member and Professor of Medicine, Chief of the Division of Rheumatology, and Vice Chair for Faculty Affairs in the School of Medicine, University of California, Los Angeles, echoed Dr. Raisz's comments regarding intervention trials. She explained that an intervention that involves administering losartan to patients with Marfan's syndrome would be a "no-win" situation, because the study would face criticism ethically from a human subjects concern perspective if not all of the study participants receive the drug. If, however, all patients receive the drug, then the study faces criticism for not being a double-blind, placebo-controlled study. Creative thinking is needed to more logically manage human subjects concerns on these types of grants. Dr. Katz added that the losartan example is an unusual one in that it involves a drug that is already on the market.

Dr. Jacobs asked if those individuals conducting human subjects research under Type 1 R01 grants who do not apply for Type 2 funding are lost to the system, not applying for any subsequent applications, or not submitting a Type 2 application for their particular grant. Dr. Martin indicated that a small percent do come back for competing renewal. There is an approximate 5 percent drop-off among PIs conducting human subjects research compared to those conducting non-human subjects research in terms of applying for grants outside of the original R01. The data system is structured such that it is not possible to determine whether R01

PIs return as co-PIs on other grants. Dr. Joan McGowan, Director of the NIAMS Musculoskeletal Diseases Branch, noted that in her experience, many clinical applications that are designed to address a specific question answer that question during the tenure of the grant. In these cases, the PIs would not be applying for Type 2 grants.

Dr. Hahn noted that it would be interesting to run an analysis to determine the proportion of researchers who have a successful Type 1 R01 and then leave NIH-funded research to have a project in that same area funded by industry. Researchers who answer questions of interest to the pharmaceutical industry and move to that sector generally have more attractive timeframes and funding to take that work further. Dr. Hahn added that this could be regarded as a measure of success in that the investigator is not lost to the field of human subjects investigation, but rather has expanded to another funding source that is not captured in NIH data. Dr. Raisz added that the dropout of clinical investigators often is due to the fact that the first hypothesis they tested did not work out. Another interesting analysis would involve determining what non-renewing PIs got out of their initial clinical research project in terms of a result (e.g., finding out how many failed). Dr. Stanley concluded the discussion session by noting that over the last 10 years, conducting clinical research has become increasingly difficult because of burdensome regulations that can discourage investigators. This also may be a factor in why some PIs do not reapply for NIH funding.

VI. CLINICAL RESEARCH POLICY ANALYSIS AND COORDINATION PROGRAM: FOSTERING SIMPLICITY, CLARITY, AND EFFICIENCY IN CLINICAL RESEARCH POLICY

Dr. Amy Patterson, Director of the NIH Clinical Research Policy Analysis and Coordination (CRpac) Program, noted that the clinical research enterprise is rapidly expanding in scope and complexity. For example, clinical research projects are no longer solely local endeavors of large academic medical centers. As the landscape has grown in complexity, so have the requirements for the conduct and oversight of clinical research. Growth has occurred by accretion and in a fragmented manner, and many oversight policies still reflect a time when clinical research was a local enterprise. As a result of this evolving research paradigm, investigators and Institutional Review Boards (IRBs) face many challenges, such as: (1) multiple layers of local and federal review, (2) highly variable and redundant requirements to fulfill similar reporting needs and oversight mandates, (3) confusion over definitions and terms, and (4) questions about the proper interpretation of certain requirements.

To address these challenges, the NIH recently launched the CRpac Program, with the goal of promoting clear, effective, and coordinated policies and regulations for the conduct and oversight of clinical research; and maintaining the integrity and enhancing the effectiveness of federal and institutional systems of oversight. NIH imposes a number of policies and requirements based on the type of research being conducted (above and beyond the regulatory baseline). As a member of the federal family, NIH sees, well in advance, many of the policies, rules, requirements, and regulations that ultimately go through and are endorsed by the Department of Health and Human Services (DHHS). Dr. Patterson explained that CRpac works in concert with sibling agencies and research communities to catalyze the federal-wide coordination of policies pertaining to

clinical research. The Program also develops tools and resources to facilitate understanding of and compliance with clinical research policies and requirements.

A number of high-priority issues were identified during the NIH Roadmap consultation process. These include: (1) diversity and adverse event reporting requirements; (2) clinical trial data and safety monitoring; (3) applicability of privacy requirements and the Health Insurance Portability and Accountability Act to clinical research; (4) appropriate models of IRB review; (5) best practices in informed consent requirements; (6) variable interpretation of human subjects regulations; and (7) science, safety, and ethics in clinical trial design. In response to concerns identified with the PIs of NIH-funded research, CRpac is considering a number of issues and has undertaken a number of activities.

The first and highest priority for CRpac on the list identified during the NIH Roadmap consultation process is adverse event reporting, particularly the divergent federal reporting policies that differ not only in terms of the scope of what is reportable, but also on the threshold and timeframe for reporting. This divergence creates confusion, non-compliance, and increased costs; the quality of the information is poor; there is a deluge of adverse event reports that cannot be interpreted in multisite trials; and a potential for negative effects on the protection of human subjects. To address these complex issues, a Federal Adverse Event Task Force (FAET) was formed with the charge of proposing specific means for promoting harmonized and streamlined federal requirements for reporting, analyzing, and communicating adverse events in clinical research. Member agencies include the FDA, Office for Human Research Protections (OHRP), Agency for Healthcare Research and Quality (AHRQ), Department of Defense, Veterans Administration, Centers for Disease Control and Prevention (CDC), and NIH (serving as Chair of the Task Force). Three FAET objectives have been identified:

- Agencies will speak the same language (by reducing variability in terms and definitions and aligning federal adverse event reporting policies).
- There will be one core adverse event report that PIs can send to multiple agencies. This Basal Adverse Event Report (BAER) will include a baseline set of core medical information adopted by all agencies and will incorporate DHHS standards for data transmission and vocabularies.
- The Task Force will develop a best practices blueprint for reporting, analysis, and application of safety information.

Dr. Patterson described the BAER in detail, noting that approximately 4,000 data elements the federal government collects regarding safety information have been identified. Many of these data elements are redundant, and in consultation with partner federal agencies, roughly 300 unique concepts or data elements have been identified that the agencies agree are integral components of any adverse event reporting that is acceptable. Some of the key features of the BAER are that it draws on existing data standards for adverse event reporting and encompasses behavioral and social sciences research, epidemiologic and surveillance studies, and health services research.

Through use of the BAER, investigators will be able to draw upon a single, streamlined data set to report safety information to multiple agencies, report unanticipated problems, and report to IRBs and Data Safety Monitoring Boards (DSMBs). Most importantly, the BAER holds the potential to enhance the protection of human subjects by providing standards that enable a more uniform and streamlined approach to adverse event reporting by promoting the completeness of data, improving the quality of data, and facilitating analysis of information. FAET members agree that the draft BAER represents a single, baseline set of core information acceptable to their respective agencies, and that it contains the information needed for adverse event and unanticipated problem reporting across all types of clinical research. The first phase of federal implementation is expected in late 2007.

Another, related issue being tackled by CRpac is determining how NIH addresses emerging safety reports about drugs that are currently being used in NIH-funded clinical trials. As a matter of policy, all NIH clinical trials must have a data safety monitoring plan, and certain types of studies require a DSMB. There is a need to clarify when DSMBs are necessary, the roles and responsibilities of DSMBs with regard to other clinical trial monitoring mechanisms, and best practices and standard operating policies and procedures.

A number of science, safety, and ethical issues surrounding clinical trial design are being considered by CRpac. Dr. Patterson noted that proper trial design is critical to ensuring the scientific validity, safety, and ethics of clinical research. Different design choices have different implications for the applicability of research results to clinical practice. In partnership with a number of federal organizations, the NIH co-sponsored a highly successful meeting attended by several thousand participants titled “Usual Care in Clinical Research: How, When, and Why?” The meeting discussed how, when, and why researchers incorporate a “usual medical care” arm in the design and conduct of randomized clinical trials.

Another issue identified for consideration by CRpac is optimizing IRB review models in light of an evolving research landscape (e.g., the growing prevalence of multicenter trials). IRBs were established at a time when primarily large academic institutions conducted clinical research. Historically, IRBs were: (1) conceptualized at a time when primarily large academic institutions conducted human research; (2) conceptualized as a local, institutional body; and (3) obligated to consider the local context. As research has become increasingly collaborative, more multisite trials are being used, and people are more interested in looking at central or other alternatives to local review. These are attractive not only for their efficiency and consistency, but also for their expertise that might not be present at the local site. As a result, a number of alternative IRB models have emerged. These include commercial IRB review (e.g., Western, Chesapeake); reciprocal IRB review (e.g., MACRO); consortia IRB review (e.g., BRANY); and facilitated IRB review (e.g., NCI CIRB). Despite the potential advantages of centralized review, institutions are resisting adoption of alternative IRBs due to a number of issues such as liability concerns, the desire for local control, and a misunderstanding of federal policies. An invitation-only workshop was held in 2005 that explored optimal models of IRB review for various research contexts. This 2.5-day workshop resulted in potential draft strategies to overcome those barriers. An executive report of the findings was presented to the Secretary’s Advisory Committee on Human Protections and formed the framework for an upcoming national conference (the National Conference on Alternative IRB Models: Optimizing Human Subject Protection) that will focus

on: (1) shared responsibility between institutions and IRBs; (2) characteristics of alternative IRBs and impact on quality of review; (3) liability issues; and (4) economic considerations.

CRpac also is addressing the concept of enhancing scientific and public access to clinical trials information, focusing on the issue of what steps the NIH should take to enhance access, particularly to information about unpublished studies with negative or neutral results. Enhancing access to NIH funded trial results would enable investigators to build on a more complete body of established work, allow for optimization of design of clinical trials, enhance the safety and protection of study subjects, and improve program planning and portfolio management. In working on this issue, CRpac is helping to link trial results to ClinicalTrials.gov, and is conducting an in-depth study on issues regarding unpublished trial results.

In terms of research using specimens and data repositories, there is disharmony in regulations and policies that creates barriers to biobanking and sharing data. Guidance is needed to clarify complex issues such as ownership, intellectual property, and the return of research results. Dr. Patterson's office has formed a trans-NIH task force to address a common framework for addressing ethical, legal, and social implications issues. NIH also chairs a departmental-level task force that includes OHRP, FDA, AHRQ, CDC, and is working toward development of more consistent policies.

In discussing the centralized collection of phenotypic and genotypic data, Dr. Patterson explained that genome-wide association studies, large-scale studies of genetic variation across the genome to identify associations with disease, will provide new targets for prognostic, diagnostic, therapeutic, and preventive strategies. There is broad interest across the agencies for this work, particularly in terms of cardiovascular diseases, cancer, and autoimmune and rheumatologic diseases. The premise is that data sharing is particularly critical because there are powerful opportunities resulting from comparisons across multiple studies. These studies are resource intensive, and a number of analytical challenges are involved. Other challenges include trial design, data analysis, data standards and formats, access policies, protecting study subjects and data, publication policies, and intellectual property. NIH recently published for public comment a potential new policy to promote sharing, including encouragement of early release of data and development of a central database, consistent with human subject protections. This draft policy can be reviewed online at www.reffectcomments.org/GWAS/.

Finally, Dr. Patterson touched on the issue of privacy and confidentiality, asking the question: "Is the Health Insurance Portability and Accountability Act Privacy Rule adversely affecting clinical research?" There is a need for more systematic information regarding the impact of the Rule outside of anecdotal evidence. There is a movement within the federal government to revisit the privacy rule with a potential eye toward helpful revisions, and the NIH is engaged in looking at strategies for gathering more systematic information regarding the impacts of the Rule on clinical research. Dr. Patterson concluded her comments by inviting Council members to visit the CRpac Web Site at <http://crpac.od.nih.gov>.

Discussion

In response to a question from Dr. Hahn, Dr. Patterson explained that FDA will endorse the BAER as a unified format for submission of adverse events, both pre- and post-market. She added that there are differing schools of thought on how the government should proceed in terms of implementation. Dr. Raisz asked if her group has considered tackling the issue of diagnostic terms and consolidation of diagnostic terms. Dr. Patterson replied that CRpac's efforts currently focus on agreeing on what the reportable elements are to describe what has happened to a patient. A unified vocabulary and common terms for describing toxicities are under discussion, but agreeing what the data elements are is the first step; the next step is agreeing on what the language will be to describe those elements. Dr. Katz noted that the toxicities present a challenge; toxicities for widespread metastatic melanoma would be viewed differently than the toxicities for the patient who has acne or arthritis.

Dr. Hahn noted that the NIH is not free from the problems associated with IRBs, giving examples from her research, where 6-8 months are needed for a proposed patient consent form to be cleared at the NIH so that it can be submitted for the first time to her institutional IRB, which then can take 6 months or more to review it and potentially suggest revisions. Dr. Katz agreed that the IRB issues are not totally external to the NIH.

Dr. Raisz asked whether CRpac considered DSMB groups from industry in their analysis of DSMB functions at NIH, noting that there may be lessons learned by examining the focus and pressures faced by industry DSMBs. Dr. Patterson indicated that CRpac has had some informal discussions with industry, and these DSMBs will be more involved in CRpac activities in the future. Radiologist, patient advocate, and Council member Dr. Gena Carter asked about the term "microdosing phase 0." Dr. Patterson explained that this references a recent movement at FDA to allow small, almost homeopathic doses of drugs without the usual types of regulatory oversight and small numbers of subjects. These studies are primarily designed for safety and proof of concept.

VII. CAREER AWARDS FOR SURGEONS

Dr. James Panagis, Program Director of the Orthopaedics Programs within the NIAMS Musculoskeletal Diseases Branch, reviewed the Institute's support of career awards for surgeons whose clinical or research activities involve musculoskeletal tissues and skin. He brought to the Council's attention the fact that NIAMS is aware that the surgeon community may be facing increasing hurdles in the ability of its younger faculty members to submit career awards to NIH. Dr. Panagis described the following three major goals of the career award program:

- Create diverse pools of highly trained scientists available in adequate numbers and in all research areas of interest to the ICs. The surgical community has a unique knowledge base and insight that are necessary for NIAMS, as the Institute supports and promotes research to improve musculoskeletal and skin health; these communities have to be active players in that enterprise.
- Provide mentored research experiences in both basic and clinical research.

- Train a cadre of clinician surgeon scientists who will become independent and productive researchers.

Dr. Panagis discussed key features of the Mentored Career Awards, which specifically target clinicians who want to be basic and/or clinical researchers. The awardee has to be a U.S. citizen, non-citizen national, or permanent resident. Federal policies allow that salaries for these awardees can be supplemented by the Institution or outside sources, but not by federal grant dollars. These mentored career awards generally require a 75 percent level of effort (e.g., 30 hours out of a 40-hour work week), and these awards generally are not renewable. Dr. Katz noted that NIAMS' definition of a work week does not always hold in medical schools and academic health centers; many institutions do not limit the work week to 40 hours.

Dr. Panagis noted that there are four major mechanisms available to clinicians that can serve as career awards: (1) the K08 is a mentored award for clinicians who want to learn basic or bench-top research, (2) the K23 is another mentored award for those who want to learn how to conduct patient-oriented or clinical research, (3) the K24 is a mechanism for clinicians who are in mid-career and already doing clinical research, and (4) the K99/R00 is the new NIH Pathway to Independence Award, and it is a combination of a mentored experience at one of the NIH research laboratories and R01 funding at the investigator's institution of choice. Dr. Panagis focused the remainder of his presentation on the K08 and K23 mentored awards, which provide 3-5 years of support, a salary of \$75,000, research support ranging from \$20,000-\$25,000, and a requirement for a 75 percent level of effort.

Dr. Panagis noted that in NIAMS' experience, surgical communities not only submit fewer grant applications, they also receive fewer awards. Across all of NIH, the success rate for the K awards is roughly 40-45 percent. Dr. Katz added that surgeons apply for these awards in much smaller numbers than do other communities. Possible barriers to submission include board certification requirements, maintaining procedure competency, educational debt because of protracted training, the required level of effort, and salary/overhead/departmental issues. Young investigators typically work in busy departments. For them to take time and work in the laboratory or conduct clinical research generally requires having someone else in the department covering their time. Another departmental pressure facing young investigators is the mentality at many academic centers, where young investigators who are not initially successful in getting a research award are encouraged to forgo their research careers.

Three other NIH ICs have noted similar decreased application rates amongst surgeons in their communities, and have taken steps to address it. For example, the National Eye Institute (NEI) does not impose any special cap on salary requests for the K08 and K23 awards. The NEI will pay 75 percent of an awardee's institutional salary up to the NIH R01 maximum, which is currently \$183,500. The NHLBI has two initiatives; the first is a new pilot program for the K08 and K23 awards that decreases the level of effort to 50 percent for cardiothoracic and vascular surgeons. NHLBI also has entered into a Memorandum of Understanding (MOU) with both the American Vascular Association and the Thoracic Surgery Foundation for Research. These outside entities have agreed to pay \$75,000 of additional salary for the awardees. As part of this agreement, clinicians submit applications to both NHLBI and these outside entities; applications

then undergo independent reviews. The American Vascular Association and the Thoracic Surgery Foundation for Research support 2-3 joint awards per year for K08 and K23 awardees.

Similarly, the National Cancer Institute (NCI) entered into MOU relationships with the American Urological Association's Foundation for Research to support K08 and K23s. The NCI has provided both supplemental salary support for the first year of the award, and has decreased the level of effort for the investigator to 50 percent. The NCI also has an MOU in place with the Thoracic Surgery Foundation for Research for K08 and K23 awards. As part of this agreement, the Thoracic Surgery Foundation for Research provides additional salary support over the \$75,000 cap towards that individual's normal institutional salary, with the same \$183,500 as the maximum allowable amount. This collaborative arrangement also includes joint applications, independent reviews, up to 5 years of support, and provides support for 1-3 supplemental awards per year.

Dr. Panagis asked Council members to consider and discuss the following options NIAMS has for enhancing the receipt of career award applications from surgeons:

- Increasing the salary cap towards the applicant's institutional salary.
- Reducing the required time commitment (level of effort).
- Encouraging public/private partnerships with medical or voluntary groups to provide supplemental salary support (not from federal grant dollars).

Discussion

Ms. Carmen Cheveres DeMummy, patient advocate and Council member, asked Dr. Panagis when it would be most appropriate to encourage adding extra dollars to these awards through public-private agreements. Dr. Panagis explained that for NIAMS to do so, it would first require entering into a formal agreement with an outside entity that clearly lists what each party would do, allows the outside entity to specify what the supplemental salary would be, and indicates the number of awards this entity would be willing to supplement. Dr. Katz added that NIAMS currently has this type of arrangement for an individual training grant with the American Skin Association that supplements the grant by \$30,000 as well as with the Orthopedic Research and Education Foundation. He noted that the Institute cannot solicit those types of arrangements; the outside entities have to approach NIAMS.

At prior Council meetings, increasing the salary cap for K awards has been discussed—doing so would result in decreasing the success rates for these awards. Dr. Katz asked Council members to provide input on the possibility of reducing the time commitment, which can be implemented much more easily than the other two options presented by Dr. Panagis.

Dr. Jacobs noted that this issue is repeatedly discussed within the orthopaedic community. One common observation from young investigators when they are encouraged to apply for these K awards is the impediment of the time commitments. The "30-hour rule," which is interpreted differently at NIAMS and medical centers, is a barrier. Dr. Jacobs added that it is very difficult

for a surgeon to spend 75 percent of a 60-hour work week doing research while still being clinically active. As a procedure-based specialty, there has to be a certain number and volume of cases worked to maintain competence. He strongly encouraged NIAMS to follow in NHLBI's footsteps, and indicated that NIAMS likely will see an increase in applications if the level of effort requirement is decreased.

Dr. Stanley asked whether it would be possible for these K awards to include funding for a staff support person for the awardees. He noted that the awardees are highly trained experts who do not want to spend their time populating a database, filling out the necessary forms and applications, and so on. These administrative/technical tasks can be a barrier to individuals applying. Having a technical person to help investigators interface with the research community, assist with data collection, and help address regulatory requirements would be a big plus to potential applicants for these awards. Dr. Katz indicated that there is some money included in these awards for this type of support, if the investigator wishes to use these funds in this manner.

Dr. Hahn asked about changing the level of effort requirement to a set number of hours rather than a percentage of the work week. Dr. Katz indicated that there is an obstacle within NIH for converting the level of effort requirement from a percentage to an exact number of hours—he will provide Council members with additional information on this issue at a future Council meeting. Despite this challenge, it is possible to reduce the overall time commitment without having to convert a percent time to a discrete number of hours. Dr. Hahn noted that at her institution, surgeons are no longer the major income generators at the hospital or within the department of medicine. If this is true on a national level, the need for NIH to support researchers in surgery will become more and more critical, because extra funds to set up independent laboratories at these institutions are not there anymore.

Council member Dr. Randy Rosier, Professor in the Department of Orthopaedics at the University of Rochester Medical Center, agreed that decreasing the percent level of effort requirement would be an extremely positive step and one that would have the most impact. He suggested that board certification requirements may not be a barrier to surgeons applying for these awards, explaining that unlike many other surgical boards, the American Board of Orthopaedic Surgery does not require a specific number of cases. There is a requirement for a 2-year period of practice at the same location, but any level of clinical practice is satisfactory. The Board has been flexible in allowing individuals to accumulate cases to generate their case lists over split periods of time in the past and would likely be accommodating and flexible as needed. Dr. Rosier also explained that a 50 percent level of effort for many subspecialties in orthopaedics can generate a self-supporting practice. At a 75 percent level of effort, the feasibility drops off, particularly for young surgeons trying to build a practice. He commented that the idea of supplemental partnerships with other organizations is a good one, but to get any traction over time, it has to be a long-term, ongoing commitment so that the institutions and individuals can become aware of it and consistently apply for it. Dr. Martin Kushmerick, Professor in the Department of Radiology at the University of Washington and a member of the NIAMS Advisory Council, also voiced strong support for reducing the level of effort, noting that he is consistently told that the 75 percent requirement is a barrier to potential applicants.

Dr. Kotzin expressed concern about whether reducing the level of effort will fix the problem, and asked whether the fundamentals of conducting good science are being skipped in providing these awards. He asked about how additional activities could be built into these awards, such as training. Dr. Katz noted that the K23 award has a requirement for coursework. Dr. Kushmerick indicated that these awardees want to put the time in to fulfill the level of effort requirement; however, they cannot afford to do so at the local university level, because at the 75 percent level of effort, it effectively limits their total work time.

Dr. Raisz raised the issue of equity, noting that whether or not a clinician is in a lucrative practice should have no bearing on compensation for research. Dr. Katz noted that should NIAMS adopt a policy reducing the level of effort while keeping the salary structure as it stands now, it would be consistent with how other ICs (e.g., NHLBI, NCI) have tried to encourage more surgeons to apply for these awards. Dr. Katz asked Council members for a show of hands on whether they would be in favor of reducing the time commitment to a 50 percent level of effort (as opposed to a 75 percent level of effort) while maintaining \$75,000 in salary support for all surgeons. Eight Council members indicated that they would be in favor, four that they would be against, and the remaining Council members abstained.

VIII. NIAMS IRP DIRECTOR'S REPORT

Dr. John O'Shea, NIAMS Scientific Director, provided an overview of the NIAMS IRP. The Program includes a total of 18 senior investigators. Including staff scientists and staff clinicians, the IRP has about 25 faculty members. Dr. O'Shea presented the research interests of these faculty members in the following components of the NIAMS IRP: Arthritis and Rheumatism Branch, Autoimmunity Branch, Molecular Immunology and Inflammation Branch, Genetics and Genomics Branch, Office of the Clinical Director, Laboratory of Structural Biology, Laboratory of Muscle Biology, Cartilage Biology and Orthopaedics Branch, Developmental Skin Biology Unit, and Protein Expression Laboratory. Also within the NIAMS IRP is the Office of Science and Technology, which has the following cores: Biodata Mining and Discovery Section, Engineering and Instrumentation Unit, Flow Cytometry Section, Laboratory Animal Care and Use Section, Light Imaging Section, X-ray Crystallography Section, and Career Development Section.

Dr. O'Shea briefly touched on the following highlights from the IRP in the last year:

- The Kastner laboratory works on autoinflammatory disorders, and has published a paper in the *New England Journal of Medicine* on the treatment of NOMID with anakinra.
- The Ward laboratory has had a number of papers published this year, including work on systemic lupus erythematosus outcomes (the *Journal of Rheumatology*), prediction of mortality in systemic lupus erythematosus (*Arthritis and Rheumatism*), risk factors in ankylosing spondylitis (*Arthritis and Rheumatism*), and measuring function in rheumatoid arthritis (*Arthritis and Rheumatism*).
- The O'Shea laboratory published a paper on regulation of Th17s (*Nature Immunology*).

- The Rivera laboratory published work on cholesterol deficiency in Smith-Lemli-Optiz syndrome and increased mast cell responsiveness (*Journal of Experimental Medicine*). They also published a paper on activation of sphingosine kinases in the *Journal of Biological Chemistry*.
- The Lipsky laboratory published work on memory T cells in systemic lupus erythematosus (*Arthritis and Rheumatism*) and on TNF control of human T regulatory cells (*Blood*).
- The Plotz laboratory published a paper on autophagy and lysosomes in Pompe disease (*Annals of Neurology*) as well as a paper on risk factors in inflammatory myopathies (*Medicine*).
- The Siegel lab had a paper on ER retention and signaling by TRAPS TNFR1 mutants published in the journal *Blood*.
- Three published works from the Sartorelli lab include studies on the recovery of dystrophic muscles by deacetylase inhibitors (*Nature Medicine*), follistatin induction and myoblast fusion (*Journal of Cellular Biology*), and Fgfr4 and muscle regeneration (*Journal of Biological Chemistry*).
- The Tuan laboratory published a study in focusing on genes regulating mesenchymal stem cell self-renewal and multipotency (*Stem Cells*).
- The Wang laboratory published work on titin as a giant scaffold for integrating stress (*Journal of Biological Chemistry*).
- The Morasso laboratory published work on Dkk2 corneal epithelial development in the journal *Development*.
- The Steven and Wingfield laboratories collaborated on a number of projects and recently published work on epitope diversity of hepatitis B virus capsids (*Journal of Molecular Biology*).

Dr. O'Shea explained that one of the greatest needs in the NIAMS IRP is promoting clinical and translational research. In that regard, the NIH Clinical Center is a tremendous resource, one that the NIAMS IRP plans to take advantage of—part of the IRP's goal is to ensure that it is making adequate use of the Center. The IRP also plans to convert Dr. Michael Ward to tenure, and hopes to recruit an orthopaedic surgeon (three candidates have been interviewed so far). In addition, there have been discussions with the President of the Uniformed Services University of the Health Sciences to consider avenues for future collaboration. Dr. O'Shea explained that Dr. Juan Rivera of the NIAMS IRP is heading efforts in trans-NIH intramural initiatives to examine ways that NIH scientists could work together on new and different projects.

The NIAMS IRP faces the challenges of having an Institute with diverse interests, stemming from the history of NIAMS and how it was created. With these diverse issues, promoting cohesion can be difficult, and is a priority for Dr. O'Shea in his role as Scientific Director of the

Institute. NIAMS has a number of strengths that cut across the different subject areas, including transcriptional regulation, signal transduction and receptor biology, and structural biology. The NIAMS IRP sponsors a popular Friday Seminar Series, and there are other efforts underway to promote interactions between clinicians and basic scientists.

Dr. Dan Kastner, Clinical Director of the NIAMS IRP, discussed the NIAMS Intramural Program in Translational Research. NIAMS IRP leadership considers it a top priority to take advantage of the unique resources available on the NIH Campus in terms of the Clinical Center and in particular to develop a translational program that ties together laboratory-based activities with clinical activities to yield a unified, translational approach. There is a 20-year tradition of translational research at NIAMS; Dr. Kastner presented highlights of these efforts, including:

- Landmark clinical trials establishing the efficacy of cyclophosphamide in the treatment of lupus nephritis.
- Studies of the history, pathogenesis, and treatment of polymyositis and dermatomyositis.
- Discovery of the genes causing a number of Mendelian disorders of the skin.
- Identification of Jak3 mutations in severe combined immune deficiency, and development of Jak3 antagonists as a new class of immunosuppressive drugs.
- Studies of systemic autoinflammatory diseases.
- Identification of the gene for familial Mediterranean fever.
- Description of the TNF receptor-associated periodic syndrome (TRAPS).
- Identification of mutations in the protein that causes NOMID.
- Use of cytokine inhibitors of TRAPS and NOMID.

Dr. Kastner provided detailed descriptions of the studies that found that the drug anakinra brings marked improvement in both symptoms and inflammation underlying NOMID as an example of activities for which the Clinical Center can be utilized. Other areas of active investigation at the NIAMS IRP include studies of the inflammatory myopathies, lupus, and vitamin D deficiency.

Dr. Kastner also discussed the Program in Translational Research, which has the mission statement: “To facilitate patient-oriented intramural research in the areas of arthritis, musculoskeletal and skin diseases, including their genetic inflammatory and immune mechanisms.” Program priorities include: (1) investigations into the pathophysiology of human disease; (2) studies of conditions for which it is difficult to assemble adequate cohorts in academic health centers; (3) innovative interventional trials in serious disorders for which adequate treatment options do not exist; (4) studies capitalizing on the sophisticated imaging and laboratory technologies available at the NIH Clinical Center; and (5) development of trans-institutional initiatives in translational research.

In terms of the structure of the Program in Translational Research, there are three main components: (1) Laboratory of Clinical Investigation; (2) Arthritis and Rheumatism Branch; and (3) Clinical Research and Training Branch. Dr. Kastner discussed ongoing recruitment efforts for the Program, including a pediatric rheumatology physician scientist, adult rheumatology physician scientist, and a clinical trialist.

There is an counterpart to the NIH Roadmap occurring on the global NIH intramural level. Several months ago, the intramural research programs at NIH ICs were asked to provide input on new directions that might be cross-cutting, trans-Institute approaches to conducting research. As noted by Dr. O'Shea, Dr. Rivera is heading part of that effort. NIAMS proposed creating an interaction among Institutes that have interests in immunology, autoimmunity, inflammation, and autoinflammatory diseases. There is tremendous expertise at NIH in terms of the basic science of these diseases, and the Clinical Center can be utilized to bring in patients with these conditions. This proposed concept, known as the Interinstitute Program in Inflammation and Immunity, involves collaboration with several Institutes (e.g., NIAMS, NCI, National Institute of Dental and Craniofacial Research, National Institute of Allergy and Infectious Diseases, National Institute of Environmental Health Sciences, etc.) to focus on these diseases. This collaboration is planned on at least three levels: (1) the development of various natural history and treatment protocols; (2) sharing innovative laboratory resources for clinical samples; and (3) the creation of a new training program, the Clinical Scholars in Immunology and Inflammation, which would be a multidisciplinary training program to bring together rheumatology, allergy, immunology, infectious diseases, and other specialties into a combined training program.

Discussion

Dr. Raisz asked whether NIAMS has a training program in rheumatology. Dr. Kastner indicated that the Institute does have such a program, and the program currently includes three first-year fellows and three second-year fellows. Three fellows also are participating in the third year, which is solely dedicated to research. Dr. Stanley asked about budget implications, noting that the overall NIAMS budget was cut, yet the IRP appears to be experiencing a lot of growth. He also asked about the cost of admitting patients to the Clinical Center. Dr. Kastner explained that for the Clinical Center, there is a budgetary implication for having patients admitted, but the Clinical Center is being underutilized, and the Institute is being encouraged to admit patients appropriately for protocols. Dr. Katz added that it behooves NIAMS to use the Clinical Center as much as it appropriately can. Dr. O'Shea discussed the growing IRP in light of a decreased budget, noting that the first step is identifying inefficiencies in the IRP (e.g., trying to find more desirable contracts). The NIAMS IRP wants rigorous review of its programs, and larger programs may need to be scaled down.

IX. NIAMS CONTRACT CONCEPT CLEARANCE

Dr. Janet Austin, Director of the NIAMS Office of Communication and Public Liaison, reminded Council members that information dissemination is part of the NIAMS mission. The Office of Communications and Public Liaison communicates research advances and the latest health and science information through a range of activities. The Office currently oversees two contracts

that support services to operate two national information clearinghouses. In dealing with the public and other clearinghouse users, each of the two Congressionally-mandated national information clearinghouses has a separate and unique identity. The two clearinghouses are: (1) the NIAMS Information Clearinghouse, and (2) the NIH Osteoporosis and Related Bone Diseases ~ National Resource Center.

In 2005, the clearinghouses averaged more than 3,000 requests per month, and more than 1,000,000 publications were distributed. The primary reason people visit the NIAMS Web Site is to obtain health information, and in 2005, users downloaded more than 400,000 PDF files, a 68 percent increase from 2004. At the clearinghouses, between 50 and 75 percent of the requests are from consumers and the general public—60-80 percent of requests are submitted via the Internet or by telephone. It is now time to re-compete both of these contracts; Dr. Austin asked the Council for approval of the concept clearance, which was distributed to Council members. The proposed project will be for another 5 years.

Discussion

Dr. Katz noted that the clearinghouses are something that the Institute uses to provide an important service to the national and international communities in terms of information dissemination. Trying to do this in-house would not be feasible. Dr. Katz asked for a show of hands from Council members in favor of and opposed to this concept clearance. The concept clearance was unanimously approved, with no abstentions.

X. FY 2008 INITIATIVES

A discussion of FY 2008 NIAMS initiatives took place during closed session.

XI. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 626 applications in closed session requesting \$161,902,879 and recommended for \$161,360,482.

XII. ADJOURNMENT

The 60th 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

Deputy Director, Extramural Program
National Institute of Arthritis and
Musculoskeletal and Skin Diseases

Stephen I. Katz, M.D., Ph.D.
Chairman, National Arthritis and
Musculoskeletal and Skin Diseases
Advisory Council

Director, National Institute of Arthritis
and Musculoskeletal and Skin Diseases