National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

September 21, 2004

Department of Health and Human Services
Public Health Service
National Arthritis and Musculoskeletal
and Skin Diseases Advisory Council

Minutes of the 54th Meeting
September 21, 2004
8:30 A.M. To 4:00 P.M.

I. CALL TO ORDER

The 54th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on September 21, 2004, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 10. The meeting began at 8:30 a.m.

Attendance

Council members present

Dr. Graciela S. Alarcon
Dr. Gunnar B.J. Andersson
Dr. Bess Dawson-Hughes
Dr. Michael M. Frank
Ms. Victoria B. Kalabokes
Dr. Brian L. Kotzin
Dr. Cato T. Laurencin
Dr. Richard T. Moxley
Dr. Robert J. Oglesby (Ex Officio)
Dr. Jack E. Parr
Ms. Mary Elizabeth Replogle
Dr. Raymond Scalettar
Dr. John R. Stanley
Dr. Steven L. Teitelbaum
Ms. Sharon F. Terry
Dr. Oretta Mae Todd
Dr. Jouni J. Uitto

Council members not present
Dr. Francesco B. Ramirez
Dr. Randy N. Rosier

Staff and Guests

The following National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) staff and guests attended:

Staff

Dr. Deborah Ader
Dr. Janet Austin
Ms. Susan Bettendorf
Mr. Gahan Breithaupt
Dr. Tommy L. Broadwater
Ms. Kelli Carrington
Ms. Anne Connors
Dr. Julia Freeman
Dr. Elizabeth Gretz
Mr. Dean Guidi
Dr. Steven Hausman
Ms. Jane Hymiller
Dr. Stephen I. Katz
Dr. Cheryl A. Kitt
Dr. Charisee Lamar
Dr. Gayle Lester
Dr. Peter Lipsky
Dr. Richard Lymn
Dr. Joan McGowan
Mr. Robert Miranda-Acevedo
Dr. Alan Moshell
Ms. Melinda Nelson
Dr. Glen Nuckolls
Dr. James Panagis
Ms. Wilma Peterman
Dr. Susana Serrate-Sztein
Dr. William Sharrock
Ms. Helen Simon
Dr. Bernadette Tyree
Ms. Laura Vazquez
Ms. Eileen D. Webster-Cissel
Dr. Gary Zhang

Guests

Ms. Barbara Butler
Dr. Deborah Carper
Mr. Dale P. Dirks
Ms. Cheryl Fells

Ms. Dorrette Finch
Ms. Caroline Grabner
Dr. Sharat Kusuma
Ms. Anita Linde
Mr. David A. Lovett
Ms. Adrienne Oleck
Dr. Arnold Revzin
Ms. Michelle Rodrigues

Other NIAMS staff members and guests also were present. Dr. Stephen Katz, Director of the NIAMS, chaired the meeting.

II. CONSIDERATION OF MINUTES

A motion was made and seconded to accept the minutes of the 53rd Council Meeting, held in June 2004, with correction of the misattribution of statements to Dr. John Stanley. This misattribution was corrected in the final version of the minutes. A motion was made, seconded, and passed to accept the minutes.

III. FUTURE COUNCIL DATES

Future Council meetings are planned on the following dates:

February 8, 2005
June 14, 2005
September 13, 2005
January 19, 2006
May 25, 2006
September 28, 2006

IV. DIRECTOR'S REPORT AND DISCUSSION

NIAMShorttakes

The NIAMShorttakes this month contains information concerning Requests for Applications and other items of interest to grantees and voluntary and professional organizations working with the NIAMS. This month's Shorttakes also contains information on the Institute's long-range plans as discussed at the last Advisory Council meeting. Mr. Ray Fleming was thanked for his work in preparing the Shorttakes.

Outgoing Council Members

Outgoing Council members Drs. Gunnar Andersson, Bess Dawson-Hughes, Michael Frank, and Oretta Mae Todd were thanked for their service. Their terms ended with this meeting.

Personnel Changes at the NIAMS

Mr. Gahan Breithaupt was welcomed as the new Associate Director for Management and Operations, replacing Mr. Melvin Broadus, who served as Acting Director for 16 months. Dr. Madeline Turkeltaub, a member of the American Academy of Nursing, was welcomed as the new Clinical Coordinator for the NIAMS Extramural Program. Dr. Gary Zhang, a new Scientific Review Administrator, and Mr. Dean Guidi, a new Contract Specialist, also were welcomed.

Ms. Wilma Peterman, currently working in the Office of Program Planning, will serve as Senior Policy Analyst. She will be the key contact person for voluntary and professional organizations that work with the NIAMS in issues related to legislation. Dr. Aftab Ansari has left the NIAMS for a position at the NIH Center for Scientific Review.

Update on Budget and Congressional Activities

On June 14, the House Appropriations Committee completed its markup of the 2005 appropriations bill for the Department of Health and Human Services (DHHS). The NIH will receive $28.5 billion and the NIAMS will receive $515.4 million. On September 15, 2004, the Senate Appropriations Committee requested $28.9 billion for the NIH, 4 percent above the fiscal 2004 level and $380 million more than the President's budget request. A total of $521 million was requested for the NIAMS, a 4 percent increase over the fiscal 2004 amount.

Other Congressional Issues

Conflict of interest issues continue to be of concern to Congress and the NIH. The second meeting of the congressionally mandated and newly created Lupus Federal Working Group took place last June. Drs. Serrate-Sztein and Katz serve as co-chairs. The current status and plans of the new Biomarkers Working Group were discussed, as well as future opportunities in lupus stem cell trials in the NIAMS Intramural Research Program (IRP). The NIAMS is the lead for this working group, which comprises representatives from relevant HHS agencies and other federal agencies with an interest in lupus, as well as representatives from four lupus voluntary organizations.

Bone Health and Osteoporosis: A Report of the Surgeon General will be released soon. Dr. Joan McGowan and Dr. Lawrence Raisz, of the University of Connecticut Health Center, served as senior scientific editors for this report.

Highlights of Recent Scientific Advances

- The journal *Science* presented a review titled "Coming to Grips with Bone Loss" in the September 3, 2004 issue. The NIAMS funds many of the investigators whose work was included in this review.

- Dr. Jeffrey Chamberlain, at the University of Washington, published an article in *Nature Medicine* describing a method of gene therapy that uses an adeno-associated viral vector as a vehicle for a mini-dystrophin gene, allowing the gene to reach all damaged muscles in a mouse model of muscular dystrophy. This method represents an important advance because a major issue for all gene therapy is delivering the gene to the correct site.

- Dr. Vittorio Sartorelli, a researcher in the NIAMS IRP, suggested that treatment for the repair of damaged muscle could be based on the protein follistatin, which plays a critical role in the growth and regeneration of adult skeletal muscle cells. Dr. Sartorelli's research focused on histone deacetylase inhibitors, which assist follistatin activities, and may be important in terms of modulation or enhancement of muscle growth.

- Dr. Patrick Ross, at Washington University in St. Louis, has determined that the human immunodeficiency virus medication Ritonavir may preserve bone. In an animal model (parathyroid hormone [PTH]-induced bone loss), he showed preservation of bone using this antiretroviral medication.

- Dr. David Hunter, at Boston University, using evidence from a study of elderly Chinese, determined that using chopsticks is a risk factor for osteoarthritis in the hand. Because only one hand is used to eat with chopsticks, one hand can be compared with the other.

Highlights of Recent Activities and Plans for the Future

The NIAMS Web Site contains the NIAMS strategic plan for fiscal years 2000 to 2004. Work is currently under way for the long-range plan for fiscal years 2005 to 2009. The first planning panel on orthopaedic research met on September 21, 2004; Dr. Jack Parr, a member of the Council, attended. The next five meetings will address research on arthritis and other rheumatic diseases, skin biology and diseases, bone biology and diseases, muscle biology and diseases, and cartilage and connective tissue biology and diseases. In addition to these panels, the NIAMS will solicit input from grantees, members of the voluntary and professional groups related to the NIAMS mission areas, and the public. A notice inviting comments will be placed on the NIAMS Web site. The long-range plan for fiscal years 2005 to 2009 is tentatively scheduled for discussion at the next Council meeting in February 2005.

The NIH has been actively engaged in implementing the mandates of the Muscular Dystrophy Community Assistance Research and Education Amendments of 2001 (MD-CARE Act) and is working closely with representatives of the muscular dystrophy research and patient communities in this effort. Dr. Katz was asked to chair the Coordinating Committee. The research and education plan, developed with broad input from scientists and representatives of muscular dystrophy patient organizations, has recently been posted on the NIAMS Web Site.

As a followup to Congressional activities, the NIAMS, along with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Child Health and Human Development (NICHD) and the Centers for Disease Control and Prevention (CDC), is planning a workshop on the burden of muscle disease, to be held in January 2005; Dr. Moxley will serve as co-chair. The purpose of the workshop is to identify existing data on the cost and scope of muscle disease, particularly for the muscular dystrophies, and to recommend strategies for developing new information sources.

Programs and Activities at the NIH Level

The new Clinical Research Center opened September 22, 2004.

(1) NIH Directors Leadership Retreat

Several major topics with implications for future NIAMS activities and plans were discussed:

- Structure of clinical research at the NIH, related to infrastructure issues: Many infrastructure programs are housed in different areas of the NIH. How can these programs be better coordinated and focused, particularly within the NIH Roadmap?

- Leadership development and succession planning: This discussion concerned human resource development, focusing on how people grow in an organization and how spirit and efficiency can be increased at the NIH. A number of leadership development programs exist at the NIH and the DHHS, but more or different programs may be needed. If so, the Directors may be able to help develop these programs.

- Priority setting: This discussion focused on how Institutes undertake portfolio management and evaluation, which are affected by assessment of disease burden. A metric for disease burden evaluation should be similar for most diseases and other issues across the entire NIH; certain definitions, guidelines, and thresholds should be consistent. Members of two Institutes, the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS), discussed ways they have performed portfolio assessment and evaluation. The

NCI established a listing of its grants and a classification of the number of grants in each area of research (available at www.cancerresearchsupport.gov). The NIEHS worked with the NICHD and the National Institute on Aging to perform a publication analysis. NIAMS staff will discuss these activities with staff from the NCI and the NIEHS to determine how the NIAMS can adopt some of these metrics. The ability of the NIAMS to set priorities will be helped by accurately and specifically determining the contents of the NIAMS portfolio and identifying gaps and opportunities.

(2) Loan repayment program

The NIAMS funds two different loan repayment programs, a clinical and a pediatric program. For the clinical program, the overall success rate was 66.7 percent, including renewal applications received in 2004. For the pediatric program, the overall success rate was 46.7 percent. Considering new and renewal applications in the NIAMS, the success rate was 60.8 percent compared to the NIH-wide success rate of 56.8 percent. This program was started to reverse the loss of practitioners from certain specialties and has resulted in repopulation of these specialty fields.

(3) Public access to research data

The NIH proposal calls for researchers to submit papers describing NIH-funded research to the agency after the papers are accepted for publication and edited by the accepting journal. The proposal was placed on the NIH Web Site in early September for a 60-day period for public comments. The compromise position on the proposed policy is to make the articles publicly available 6 months after publication.

(4) NIH Roadmap activities

Dr. Deborah Ader gave the Council a brief summary of Roadmap-related activities to date.

Comments on the Director's Report

Members of the Council praised the new Clinical Research Center, which provides excellent integration of research and patient care activities along with adequate space for these activities and for support services. Patient advocacy groups provided input that was used to design the best possible environment for patients, particularly for pediatrics.

Council members asked about Clinical Research Center space allocations. Dr. Katz responded that the research housed in the Clinical Research Center must be clinically related; whole branches would not be moved en masse. A committee chaired by Dr. Edward Benz and Mr. R. Edward Howell has been established to

discuss long-range and short-range planning for the access of clinical researchers to the facilities of the Clinical Research Center and to make recommendations about investments for clinical research.

Ms. Sharon Terry and Ms. Debra Lappin have founded the Alliance for Taxpayer Access, which has met with the Federation of American Societies for Experimental Biology (FASEB), Wiley, and other commercial publishers to discuss the issues concerning public access to research papers faced by publishers and professional societies. Dr. Stanley asked how access to a research paper would be handled if an NIH-funded researcher was a collaborating author but not the senior first author on a paper. Dr. Katz commented that he believes that if the NIH contributes funds to the research, the paper would be subject to public access rules.

V. ENHANCING PUBLIC INPUT AND TRANSPARENCY IN THE NIH RESEARCH PRIORITY-SETTING PROCESS

Ms. Barbara Butler presented a report from the NIH Council of Public Representatives (COPR). The COPR was created following the release of the Institute of Medicine's report titled *Scientific Opportunities and Public Needs*, which recommended that the NIH establish a public advisory group to facilitate greater interaction between the NIH and the general public. The NIH Director's COPR was charged to advise the Director on issues affecting the broad development of NIH programs, outreach activities, and research goals. The COPR is composed of 21 members, representing many different groups and constituencies. The COPR provides a voice for public input to the NIH and the NIH Director and works to increase awareness of NIH outreach activities, programs, and resources. More information about the COPR is available at www.copr.nih.gov.

The COPR report (available at the COPR Web Site) to the NIH Director contained 11 recommendations for increasing public input into the priority-setting process for medical research. The public must be able to access and understand this process; seeking, valuing, and using public input will strengthen the public's trust in the NIH.

The following recommendations were presented at the April 2004 COPR meeting, representing some of the best practices designed to enhance public awareness of the research priority-setting process and increase the access of senior NIH decision makers to this information:

1. Encourage the NIH to go beyond the NIH campus to interact with the American public in their home communities.

2. Encourage the Institutes and Centers to use proactive outreach, actively soliciting input rather than passively awaiting public comment.

3. Encourage the Institutes and Centers to collaborate and establish more partnerships with local and grassroots organizations to provide an important conduit for public input and feedback essential for moving toward a more community-based and collaborative research process.

4. Increase cross-Institute communications through the use of working groups, progress review groups, and workshops.

5. Promote two-way communication for setting research priorities at the NIH, involving the public at the outset in a collaborative process.

6. Ensure that public input reaches senior decision makers. To be effective, public input must reach senior decision makers who must be seen as embracing the value of public input. The NIAMS Community Health Center is a good example of two-way communication.

7. Encourage the NIH to make full use of the Advisory Councils and their public members as important avenues of public input. The COPR views Advisory Councils, particularly their public members, as a valuable source of, and mechanism for, public input into the research priority-setting process.

8. Actively develop tools and materials to educate the public and enhance transparency.

9. Continue to search for easily accessible mechanisms that encourage public input into the research priority-setting process and provide information-sharing opportunities.

10. Actively solicit information from constituents and the general public about the public's experiences and perceptions of transparency at the NIH.

An example of an effective tool for educating the public and enhancing transparency is the NIH's Get Involved Web Site (www.getinvolved.nih.gov). The public liaison officers created this central NIH Web interface to provide access to information about resources and opportunities for public input and participation, covering all Institutes.

The COPR workshop titled "Inviting Public Participation in Clinical Research: Building Trust Through Partnerships," will be held October 26, 2004, on the NIH campus. More than 50 invited participants and 21 COPR members will be included. The purpose of the workshop is to provide an overview of the current status of public participation and trust in medical research, to learn about past interrelationships and proven strategies to build partnerships, and to explore barriers and opportunities for building public participation and trust. The initial

findings from the workshop will be presented to the NIH Director on October 27, 2004. The COPR and the NIH will work together to develop a draft set of recommendations for improving public participation and trust in clinical research, based on findings from the workshop. To evaluate implementation of its recommendations, the COPR plans to ask public relations staff at each Institute to provide yearly feedback on efforts to increase public awareness of NIH activities.

Comments on Ms. Butler's Presentation

Council members commented that more effort must be made to publicize the NIH in a positive way, beyond efforts that the COPR has outlined. The NBC television series *Medical Investigation* was discussed as a way for the public to learn more about what the NIH does.

A COPR committee recommended a 3-day workshop for Advisory Council public members and public participants in any NIH activities, which would provide a training session to empower public members to be more effective in their roles in these councils and to create a communication network.

Questions were asked concerning whether the COPR has resources to promote public understanding of how basic research findings can have significant implications for clinical care. The Genetic Alliance, other coalitions, and patient groups work with scientific advisors to accomplish this task.

VI. NIH PUBLIC INFORMATION AND PRESS ISSUES

Mr. John Burklow, Director of the NIH Office of Communications and Public Liaison (OCPL), spoke on NIH strategic communications. NIH Director Dr. Elias Zerhouni believes that the NIH's status as a taxpayer-funded agency requires that the public be aware of the NIH and its activities. Dr. Zerhouni has asked for development of an NIH-wide communication effort to increase awareness of the NIH and its activities, integrating all 27 Institutes and Centers into this effort.

The main objective of an NIH communication plan is to connect the science to the people. Specific recommendations are as follows:

- Make medical research more personally relevant.
- Ensure that people know that the NIH is a trusted source of information and guarantee access to this information via Web sites and other efforts.
- Explain the NIH's role in medical research, including acknowledgement of NIH support of studies reported in the media.

Specific communication strategies include the following:

- Examine the NIH infrastructure and systems. Determine simple, effective ways of promoting the NIH (e.g., use the same letterhead on press releases, include a quotation from Dr. Zerhouni in the releases), so people understand that these diverse activities are all part of the NIH.

- Be proactive, rather than reactive, with the media.

- Develop outside collaborations with patient groups and volunteer organizations.

As an example, the NIH homepage has been restructured and now uses Google as the search engine. The Health Information page and the News section have been revamped to better engage the reader. A new, 4-page NIH brochure has been developed, and the NIH Almanac also has been repackaged to be more interactive; for example, the Almanac now includes an audio presentation of Franklin D. Roosevelt's dedication of Building 1. Ongoing activities include development of an 80-page booklet that tells a more complete story about the NIH and will contain discussions by researchers about their work and the impact of their research on people. The OCPL also sponsors "Word on Health" news releases sent out to small weekly and daily newspapers across the United States and has taken a more proactive approach to media outreach, resulting in mention of the NIH on many news programs.

Recently, the NIH sponsored a press conference at the National Press Club, involving more than 50 reporters and representatives from television and radio. Accurately written articles about NIH research were presented on popular television and radio shows and in news outlets such as the *New York Times*, *Wall Street Journal*, *Washington Post*, *Science*, and *Nature*. Research! America also worked with *Parade* magazine on a cover story on young researchers. This article included a description of the NIH and explained that the NIH supported the researchers and their research.

Mr. Burklow mentioned other efforts to communicate NIH activities to the public, including public information campaigns conducted by certain Institutes and Centers; public education efforts, such as the Red Dress Campaign; the NIH Senior Health Web Site; and the "Get Involved at NIH" Web Site, hosted by the OCPL. The Office also is working with the Association of American Medical Colleges (AAMC) to plan a meeting in November at which extramural researchers will speak about their NIH-sponsored research activities.

Upcoming activities:

- The OCPL has initiated efforts to work with NBC to encourage the network to improve the accuracy of *Medical Investigation*. The CDC also has joined this effort.

- At the dedication of the Clinical Research Center on September 23, 2004, Dr. Zerhouni will participate in a satellite tour to 12 cities to speak about the importance of clinical research and the significance of the building.

- The NIH Roadmap anniversary activities will include the Pioneer Award announcement, a stakeholder briefing in mid-October, and press releases and background information on the first-year accomplishments of the Roadmap.

- The OCPL is working closely with the COPR on the COPR Public Trust Workshop.

Discussion of Mr. Burklow's Presentation

Dr. Steven Teitelbaum asked how the NIH can communicate to the public that basic research is both important and risky, but can eventually lead to significant clinical developments. The FASEB produces the Breakthrough Series, which focuses on basic research that has had clinical payoff, such as research on osteoporosis and hypertension. He also commented that 90 percent of the NIH budget goes to extramural activities, and it is crucial to the success of the NIH mission that the public (including legislators) understand that a breakthrough occurring, for example, at Johns Hopkins University may have been sponsored by the NIH. Mr. Burklow responded that efforts are under way to clarify the relationship between the extramural grantee community and the NIH, including the work with the AAMC.

Dr. Raymond Scalettar described missed outreach and communications opportunities, such as communicating with physicians and health care providers through state, county, specialty, or medical societies that could link to the NIH through their Web sites. He suggested that perhaps the NIH could develop a poster, to be placed in the reception area of physician offices, describing NIH activities. Dr. Richard Lymn suggested using diseases that affect children and teenagers to highlight NIH basic research efforts that evolve to have clinical utility. This would provide an opportunity for the NIH to develop a family outreach effort.

Mr. Burklow described efforts within his office to produce stories explaining scientific developments. For example, a story describing the science behind and development of the home pregnancy kit was featured in *USA Today*.

VII. BONE HEALTH AND OSTEOPOROSIS: A REPORT OF THE SURGEON GENERAL

This presentation was postponed until the next Advisory Council meeting.

VIII. NIH CONTRACTS CONCEPT CLEARANCE

Ms. Eileen Webster-Cissel defined concept clearance as the peer review process required for solicitations for research concepts and for proposals arriving in response to the solicitation. The concepts are not detailed statements of work because, if they were, Council members might in the future be prohibited from competing for this work. Council members will be given a general idea of concept goals, and members should assess purpose, scope, and relevance and provide feedback and recommendations to the Director regarding whether the concept should proceed. After the concept review, a solicitation for proposals will be sent out.

Dr. McGowan described a proposal to support pilot and feasibility trials in musculoskeletal diseases, which follows a previous initiative for pilot and feasibility trials in osteoporosis. The goal of the proposal is to allow studies of innovative therapies, particularly ones that would not be supported in the private sector or may not be suitable for an R01 award because of lack of preliminary data. The proposal would give investigators an opportunity to develop potential clinical trials and clinical interventions for all musculoskeletal diseases, over a 3 to 5 year timeframe.

Council members expressed concern that the proposal appears to call for trials for new indications of approved drugs, but not for trials to develop novel therapeutics. Drs. Katz and McGowan explained that the concept was meant to promote translational studies. Examples of these studies included testing electromagnetic stimulation to speed bone restoration after fracture, innovative dosing schedules for approved drugs, and trials examining the effects of combining approved drugs. These trials would provide information useful to medical professionals and consumers, but are unlikely to be sponsored by industry. Council members agreed that exploring new ways to use existing therapies was useful, but also expressed doubt that studies of dosing and scheduling were appropriate use of NIH funds.

Several members of the Council asked that the wording of the proposal be phrased to better reflect that later stage trials are being solicited, rather than phase I or II trials, as indicated in the original document. A rider was proposed calling for the language of the concept to be altered according to the discussion and for the new concept to be returned to the Council as a written document for approval within a short period of time after this meeting. A vote was taken and the rider was approved.

Dr. Moshell presented an update and proposal for innovative therapies for rheumatic and skin diseases, similar to an RFP competed in fiscal year 2002. Two investigators received funding from this program. A motion for approval of this concept clearance was made, voted on, and passed.

Dr. Lymn presented a concept clearance for continuation of the National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy (FSHD)

Patients and Family Members. The registry is one of several funded in response to an agency announcement approximately 4 years ago for diseases that could benefit from such a registry and has been very successful in focusing research on the two most prevalent forms of adult-onset muscular dystrophy. Initial work on the registry has focused on developing forms and establishing diagnostic criteria. The registry completed its fourth year in September 2004, and has been a useful platform to encourage cooperation at the national level for a clinical network in muscle diseases; eight studies are in progress using these populations. At present, approximately one-third of the target population for myotonic dystrophy and one-half for FSHD have been recruited, with help from patient advocacy groups. Barriers in recruitment have been due to complications in establishing diagnostic criteria and to the need for more aggressive outreach efforts to reach people suffering from these diseases who also may have cognitive challenges. A motion for approval of this concept clearance was made, voted on, and passed.

IX. NIAMS IRP SCIENTIFIC DIRECTOR'S REPORT

Dr. Lipsky, Scientific Director of the NIAMS Intramural Research Program, spoke on progress made in this Program in the past year, adding that this year was the 50th anniversary of the NIAMS IRP (1954–2004). Dr. John A. Hardin, from the Einstein College of Medicine, will join the NIAMS as Acting Clinical Director. Dr. Lipsky noted additional new personnel: Dr. Linda Cendales, who works on hand transplantation; Dr. Joy Blair, who works on osteoarthritis; and Dr. Rafael Casellas, who works on immunoregulation. Dr. Lipsky presented work focusing on the translational research initiative performed by some of the more junior investigators in the program.

- Dr. Raphaela Goldbach-Mansky, in collaboration with Dr. Daniel Kastner, works on neonatal onset multisystem inflammatory disease (NOMID), a congenital inflammatory disease presenting in childhood with symptoms such as fever, aseptic meningitis, destructive arthritis, skin rashes, increased intracranial pressure, and inflammatory hearing loss. The disease is caused by mutations in the *CIAS1* gene, which encodes cryopyrin, a member of a family of proteins involved in familial Mediterranean fever (identified by Dr. Kastner). Mutations in cryopyrin lead to prolonged activation of caspase 1 and increased levels of active interleukin (IL)-1 and IL-18. Based on this pathway, Dr. Goldbach-Mansky initiated a clinical trial to determine whether blocking IL-1 would improve the inflammatory symptoms occurring in this disease.

  Eleven children were treated for 3 months with an IL-1 receptor antagonist (competitive inhibitor of IL-1), and then the drug was withdrawn to determine whether blocking IL-1 activity was responsible for any effect. Plasma levels of the inflammatory proteins C-reactive protein (CRP) and a precursor of amyloid protein were measured, and both showed a decrease over the treatment period. When treatment was stopped, levels of both proteins rose. Treatment resulted in improvement of rashes and inflammation, resolution of some of the hearing loss,

and improvement of intracranial pressure. This work is helping to raise awareness of an entire spectrum of diseases that may have been previously misdiagnosed as juvenile onset arthritis. The ability to look at an individual's genetic profile, and awareness of the family of proteins that contribute to these diseases, may allow researchers to explore the genetic contributions to arthritis and how to interfere with different cytokine pathways more precisely. Using the IL-1 inhibitor to treat NOMID also is a good example of using approved drugs for new indications.

- Dr. Blair has used a mouse model of type IV osteogenesis imperfecta (OI), developed by Dr. Joseph Marini, to address whether the degeneration of cartilage seen in osteoarthritis is due to abnormalities in the cartilage or in the underlying bone. In this model, the abnormality in type I collagen indicates abnormality in bone but not in cartilage. Dr. Blair collaborated with the Animal Imaging Facility to generate images of mouse knee and used micro-CT to reconstruct the knee. By 4 months of age, OI mice show symptoms similar to those observed in osteoarthritis, including inflammation, abnormal new bone formation around the joint, disappearance of cartilage space, changes in the patella, and anterior displacement of the tibia. Some of these symptoms are observed in normal mice by 22 months of age. The OI mouse provides a reproducible genetic model showing degenerative joint changes throughout the maturation process that can serve as a model for studying the role of subchondral bone in osteoarthritis. A clinic is planned at the NIH to examine adult patients with OI to determine whether some of the joint problems they have can be attributed to rapidly progressing osteoarthritis.

- Dr. Michael Ward is conducting a number of investigations on systemic lupus erythematosus (SLE), rheumatoid arthritis, and ankylosing spondylitis, as part of an outcomes initiative in the IRP. He recently completed a study to determine whether the experience of the attending physician has an impact on outcome for patients hospitalized with SLE. He examined hospitalization records for approximately 15,000 patients with SLE in New York and Pennsylvania admitted between 1999 and 2001. The results of this study indicated that, for overall admissions for lupus, mortality rates were 4.1 percent, 3.5 percent, and 2.5 percent for patients seen by doctors who had treated less than one SLE patient per year, one to three patients per year, or more than three patients per year, respectively. Similar results for mortality from lupus nephritis were observed, with mortality rates of 12.4 percent, 7.2 percent, and 4.2 percent for the same physician experience categories. Potential confounders, including length of disease, severity, location, and comorbid conditions, were included in the analyses. Dr. Ward's work shows that a major determinant of patient outcome for these conditions is physician experience.

- Dr. Gabor Illei recently published a two-part literature review in *Arthritis and Rheumatism* to determine whether molecules measured and reported for SLE could be used as candidate biomarkers for the disease. A lack of validated

biomarkers for SLE has been a stumbling block to development of effective drugs for this condition; no new SLE drugs have been developed in the past 30 years. Several cytokines in peripheral blood appeared to be associated with SLE and may be promising for use as biomarkers, including interferon-alpha, soluble IL-2 receptor (scdc25), and soluble tumor necrosis factor receptor.

To validate molecules such as these for use as biomarkers for SLE, Dr. Terry Phillips, in collaboration with colleagues in the Division of Bioengineering and Physical Science, has developed a multiplex cytokine and chemokine analysis method, called immunoaffinity capillary electrophoresis (ICE), which may provide a platform for development of a "lupus chip" that would incorporate SLE biomarkers to allow detection of response to therapy, prognosis, and activity in SLE patients. ICE involves immobilization of the analytes of interest (present in as little as 1μl of body fluid or cell lysate) to a microcapillary tube coated with antibodies to as many as 20 to 30 different analytes. The bound analytes are labeled with fluorescent dye, acid eluted, and then separated by electrophoresis, all within the microcapillary tube. Analytes are resolved by molecular mass and can be sequenced using mass spectrometry.

This process was used to examine samples from 46 patients for the presence of 30 cytokines and chemokines and identified interferon-alpha, RANTES, and MCP-3, among others, as candidate biomarkers for SLE. ICE was then used to analyze cerebrospinal fluid, blood, and urine samples from 200 lupus patients to determine whether these cytokines associate with disease activity. There are plans to work with colleagues in the extramural community to make the ICE technique available to them or to collect large numbers of serum samples to use to validate these cytokines as biomarkers informative for lupus.

Dr. Illei also tested the ability of a humanized anti-IL-6 receptor antibody (MRA) produced by the Japanese company Chugai to block IL-6 activity; IL-6 is present in large amounts in the serum and urine of lupus patients. Data from the first 10 to 12 patients showed that the erythrocyte sedimentation rate decreases to the normal range upon treatment with MRA, but increases when treatment is stopped. MRA also reduced levels of circulating plasma cells (differentiation is dependent on IL-6), present at very low levels in normal people, but at higher levels in SLE patients. These findings provide validation that IL-6 activity is blocked in a meaningful manner, and MRA could potentially be tested in phase II trials and perhaps serve as a new therapy for SLE.

- Composite tissue allografting focuses on transplantation of peripheral tissue, including skin, muscle, nerve, tendon, and/or bone as a functional unit, such as a hand. This procedure is considered for abnormalities that are not reconstructable, such as amputations, congenital abnormalities, or destructive arthritis. At present, there are no good mechanical replacements for the hand. Dr. Cendales has been involved in the only two human hand transplants performed in the United States and is leading efforts to develop a nonhuman primate model (rhesus macaques) of

tissue allografting to study methods to maintain these allografts. During a 6-hour surgical procedure, a portion of forearm was removed and replaced with a portion from another, allogeneic monkey. To prevent rejection, researchers used an anti-T-cell serum, followed by very low doses of FK506.

For the two people who have received hand transplants, sensation returned within 6 months; by 10 months postgraft, patients had acceptable function. After a year, patients can perform complicated manipulations such as tying their shoes. In collaboration with Navy colleagues, who have treated a large number of traumatic amputations recently, the NIAMS is commencing a hand transplant program and expects to perform the first transplant by the end of the year at the Clinical Research Center.

X. NIAMS NEW POLICY FOR UNSOLICITED APPLICATIONS > $500,000 DIRECT COSTS—AN UPDATE

This presentation was postponed until the next Advisory Council meeting.

XI. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 592 applications in closed session requesting $134,730,531 and recommended for $134,730,531.

XII. ADJOURNMENT

The 54th 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.

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Cheryl A. Kitt, Ph.D. Executive Secretary, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council	Stephen I. Katz, M.D., Ph.D. Chairman, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council
Director, Extramural Program National Institute of Arthritis and Musculoskeletal and Skin Diseases	Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases