National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

February 2, 2010

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

MINUTES OF THE 70th MEETING

February 2, 2010
8:30 a.m. to 3:00 p.m.

I. CALL TO ORDER

The 70th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on February 2, 2010, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 6. The meeting was chaired by Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Attendance

Council members present:

Mr. George Beach (via teleconference)
Dr. S. Wright Caughman
Dr. Leslie Crofford
Dr. Betty Diamond
Ms. Karen Evans
Dr. Kathleen Green
Dr. Linda Griffith (via teleconference)
Dr. John H. Klippel
Dr. Henry Kronenberg
Dr. Regis O'Keefe
Ms. Jean Pickford
Dr. Clifford J. Rosen
Mr. Bradley Stephenson
Dr. H. Lee Sweeney
Dr. Julio Vergara
Dr. James Weinstein (via teleconference)

Staff and Guests:

The following NIAMS staff and guests attended:

Staff

Dr. Janet Austin
Dr. Carl Baker
Dr. Teresa Bernaciak
Dr. Michael Bloom
Dr. Amanda Boyce
Mr. Gahan Breithaupt
Dr. Eric Brown
Dr. Branden Brough
Ms. Justine Buschman
Dr. Robert Carter
Dr. Faye Chen
Mr. Ricardo Cibotti
Ms. Andrea Cimino
Mr. Richard Clark
Dr. Robert Colbert
Ms. Stephanie Craver
Ms. Wilma Peterman Cross
Ms. Robin DiLiello
Ms. Theresa Do
Dr. Jonelle Drugan
Mr. Erik Edgerton
Ms. Sharon Fair
Ms. Barbara Footer
Ms. Gerta Gallop-Goodman
Ms. Valerie Green
Ms. Gail Hamilton
Ms. Kaitaia Huynh
Ms. Katie Joffee
Mr. Andrew Jones
Dr. Daniel Kastner
Dr. Stephen Katz
Mr. Mark Langer
Dr. Gayle Lester
Dr. Helen Lin
Ms. Anita Linde
Ms. Mimi Lising
Dr. Kan Ma
Dr. Marie Mancini
Dr. Kathryn Marron
Dr. Joan McGowan

Ms. Leslie McIntire
Dr. Laura K. Moen
Ms. Regina Mong
Ms. Anna Nicholson
Dr. Glen Nuckolls
Dr. John O'Shea
Dr. James Panagis
Dr. Charles Rafferty
Ms. Natalie Reyes
Ms. Trish Reynolds
Ms. Karin Rudolph
Ms. Laurie Savage
Dr. Susana Serrate-Sztein
Dr. William Sharrock
Ms. Sheila Simmons
Ms. Theresa Smith
Ms. Allisen Stewart
Ms. Robyn Strachan
Ms Yen Thach
Ms. Jamie Thompson
Mr. Phil Tonkins
Mr. Hung Tseng
Dr. Bernadette Tyree
Ms. Marcia Vital
Dr. Fei Wang
Dr. Xibin Wang
Dr. Yan Wang
Dr. Chuck Washabaugh
Mr. Elijah Weisberg
Ms. Sara Wilson
Dr. James Witter

Guests

Ms. Jennifer Blacker, IQ Solutions, Inc.
Mr. Michael Bykowski, Consolidated Solutions and Innovations
Dr. Francis Collins, NIH Director
Mr. Chris DaCosta, PPD, Inc.
Ms. Tanya Dougans, National Heart, Lung, and Blood Institute, NIH
Ms. Ann Elderkin, American Society for Bone and Mineral Research
Ms. Patti Brandt Hansberger, Office of Legislative Policy and Analysis, NIH
Dr. John Holden, Center for Scientific Review, NIH
Dr. Laura Lee Johnson, National Center for Complementary and Alternative Medicine, NIH
Ms. Annie Kennedy, Muscular Dystrophy Association
Dr. Rajiv Kumar, Center for Scientific Review, NIH
Ms. Kimberly McGraw

Ms. Amy Melnick, Arthritis Foundation
Dr. Rebecca Minnillo, Society for Investigative Dermatology
Ms. Sheila Rittenberg, National Psoriasis Foundation
Mr. Nate Thomas, American Physical Therapy Association
Ms. Allison Trepod, SRI International
Ms. Andrea Weiss, PPD, Inc.

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept with no changes the minutes of the 69th Council meeting, held on September 16, 2009.

III. FUTURE COUNCIL MEETING DATES

Future Council meetings are currently planned for the following dates:

June 15, 2010
September 28, 2010
February 1, 2011
June 14, 2011
September 27, 2011

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz welcomed Council members, NIAMS staff, and guests. He invited attendees to review the NIAMS ShortTakes online, which include more details on many of the topics covered in his report. He noted that his "Director's Column" focuses on the NIAMS Long-Range Plan for Fiscal Years (FY) 2010-2014. The goal of the plan is to help propel research progress by informing the Institute's priority-setting process, while enabling the Institute to adapt to the rapidly changing biomedical and behavioral science landscapes. Council members were encouraged to share the plan with their colleagues and home institutions.

Dr. Katz introduced four *ad hoc* Council members:

- Dr. Regis O'Keefe, Chair of the Department of Orthopaedics and Rehabilitation at the University of Rochester Medical Center

- Jean Pickford, Executive Director of the Foundation for Ichthyosis and Related Skin Types

- Bradley Stephenson, J.D., founder of the firm Bradley R. Stephenson, Attorney at Law, and an advocate for muscular dystrophy

- Dr. Julio Vergara, Distinguished Professor in the Department of Physiology at the University of California, Los Angeles School of Medicine

Personnel Changes at the NIH/NIAMS

Dr. Katz noted with sadness the passing of Dr. Lawrence Shulman, who died in October at the age of 90. Dr. Shulman was a leader in the field of rheumatology research; in 1974 he discovered eosinophilic fasciitis, a connective tissue disorder that is known today as Shulman's syndrome. As the first NIAMS Director from 1986-1994, he guided the development of the Institute through its formative years.

Dr. Laura K. Moen was introduced as the new Director of the NIAMS Division of Extramural Research Activities (DERA). As DERA Director, Dr. Moen will serve as the Executive Secretary for the NIAMS Advisory Council and will be responsible for other key scientific management functions, including oversight of the Scientific Review Branch, Grants Management Branch, and clinical research coordinators. Dr. Moen has been at the NIH for 10 years and previously served as a Program Official in the Division of Extramural Research within the National Center for Complementary and Alternative Medicine. Dr. Katz thanked Dr. Susana Serrate-Sztein, Director of the NIAMS Division of Skin and Rheumatic Diseases, for serving as the Council's Executive Secretary prior to Dr. Moen's appointment.

Ms. Gerda Gallop-Goodman has joined the NIAMS Office of Communications and Public Liaison (OCPL) as a writer/editor for the Institute's communications efforts and as a community outreach specialist for OCPL's Multicultural Outreach Team. Dr. Teresa Bernaciak, an NIH Presidential Management Fellow, will be joining the NIAMS Office of Science Policy and Planning. She will fill in for Dr. Louise Rosenbaum, a Science Policy Analyst in the NIAMS Office of Science Policy and Planning, who is on a two-month assignment with the U.S. Department of State's Embassy Science Fellows Program.

Dr. Leon Nesti has joined the NIAMS as a Guest Researcher in the NIAMS Intramural Research Program Cartilage Biology and Orthopaedics Branch. Dr. Nesti has most recently served as a fellow in Hand and Upper Extremity Reconstructive Surgery at Walter Reed Army Medical Center and as an Assistant Professor in the Department of Surgery at the Uniformed Services University of the Health Sciences. Dr. Nesti was a postdoctoral fellow with the NIAMS from June 2004 to June 2005.

Up**date on Budget and Congressional Activities**

Dr. Katz presented a slide showing NIAMS funding trends for the past 16 years. In FY 2009, the NIAMS funded 238 new and competing continuation applications for a success rate of approximately 20 percent—a figure slightly lower than last year's rate of 20.9 percent (the overall NIH success rate is estimated to be 21 percent). Overall for FY 2009, the Institute funded roughly 1,000 total research project grants and awarded through the 15th percentile. In recent years, the Institute has emphasized maintaining a consistent percentile so that success is not dependent upon what cycle or year in which an investigator applies. From 1994 to 2002, the

NIAMS success rate averaged 5-10 percent lower than the NIH average; however the Institute has now reached a point at which its success rate (anticipated to be 19 percent this year) is very close to the NIH average.

For the NIH overall, the 2010 budget was increased 2.3 percent (or $31.2 billion). The NIAMS budget increased 2.7 percent over last year, from $524.9 million in FY 2009 to $539.1 million in FY 2010. In accordance with NIH policy, a 2 percent inflation allowance is provided for NIH investments in research supported by research grants. Dr. Katz noted that all established paylines and funding policies for the NIAMS are available on the NIAMS Web site.

As has been the case in previous years, the NIH and its Institutes and Centers will give funding priority to new investigators; the NIH goal is to equalize the success rates between new and experienced investigators submitting new R01 grant applications. In addition, there is an NIH-wide emphasis on increasing the numbers of Early Stage Investigators. The goal is to encourage early transition to independence, and the target is for Early Stage Investigators to constitute a majority of new investigators.

The President's Budget request for FY 2011 includes a $1 billion increase for the NIH; for the NIAMS, it proposes a 3.1 percent increase, to $555.7 million. Dr. Katz commented that the NIAMS is grateful for the increase and for the President's commitment to science and research.

Dr. Katz reported that Congress has passed a series of bills that temporarily extended the programs under the Small Business Act and the Small Business Investment Act of 1958 that authorizes Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) programs. Several bills involving SBIR/STTR are at various stages of the legislative process. There is disagreement over the increase of the SBIR set aside (from 2.5 to 3.5 percent of the extramural budget) and the increase of the STTR set aside (from 0.3 to 0.6 percent).

On October 20, 2009, Representative Shelley Berkley (D-NV) introduced H.R. 3856, the Bone Health Promotion and Research Act of 2009, which would require the NIH to expand and intensify osteoporosis and related bone diseases programs. It would authorize the Centers for Disease Control and Prevention (CDC) to establish a National Bone Health Program and an Education and Outreach program. Finally, it would authorize an osteoporosis and related bone diseases surveillance program at CDC. The bill was referred to the House Committee on Energy and Commerce.

Highlights of Selected Recent Scientific Advances

- The NIAMS supports several groups that are developing and testing strategies to repair ligaments and tendons. In July 2009, a team led by Dr. Martha Murray devised a new surgical procedure that entails wrapping a collagen-platelet composite around bone-tendon-bone grafts during ACL surgical repair. Pigs that received the collagen-platelet composite had superior knee function after 15 weeks of healing, compared with those that received standard ACL repair. These short-term results provided the basis for long-term studies,

which the group is conducting with American Recovery and Reinvestment Act (ARRA) funds from the NIAMS (*Am J Sports Med.* 2009 Aug;37(8):1554-1563. Epub 2009 Mar 31).

- Dr. Ron Gelberman and colleagues are examining whether platelets and their growth factors can facilitate healing of the flexor tendons of the hand. When these researchers added platelet-derived growth factor BB while surgically repairing flexor tendons in dogs, they observed that the compound stimulated formation of cells and molecules on the surface of repaired tendons that promote tendon gliding (*J Orthop Res.* 2009 Sep;27(9):1209-1215 [published online 3/25/09]). Interestingly, there was an article that appeared recently in *Science* by David Lee and others, partly supported by the NIAMS, showing that platelets amplify inflammation via collagen-dependent microparticle production.

- Using data from the Osteoarthritis Initiative and funding from the NIAMS 2006 Clinical Trials Outcomes Instrument Development Grant Program, Dr. Sharmila Majumdar and colleagues developed a technique for analyzing magnetic resonance images that could allow clinicians to noninvasively assess the development and worsening of osteoarthritis of the knee. The discovery of osteoarthritis biomarkers could lead to shorter, more efficient trials of promising disease-modifying agents (*Magn Reson Med.* 2009 Nov 13. [Epub ahead of print]).

- NIAMS-supported scientists in the United States have teamed up with researchers in the Netherlands, Iceland, Canada, the United Kingdom, and Greece to combine bone mineral density (BMD) and genomic data from more than 19,000 people. This enabled the scientists to detect 20 single nucleotide polymorphisms (SNPs) that were consistently associated with variation in BMD—only 7 of these SNPs had been detected in previous studies. The results suggest that certain SNPs confer increased risk for low bone mass and fracture, and that the total number of risk SNPs in an individual's genome can be a useful predictor of bone health (*Nat Genet.* 2009 Nov;41(11):1199-1206. Epub 2009 Oct 4).

- Scores of studies on dietary soy and soy supplements have been equivocal because of small sample sizes and short intervention periods. Building on the lessons learned from earlier investigations, Dr. D. Lee Alekel and colleagues conducted a randomized clinical trial involving more participants and monitored them over a longer time (three years), so that investigators would be able to detect favorable changes in bone health, and detrimental side effects, in response to isoflavone treatment. Although restricted to specific doses of soy isoflavone extracts, results from this study do not support the view that soy isoflavones have a protective effect on bone loss for postmenopausal women (*Am J Clin Nutr*. 2010 Jan;91(1):218-230. Epub 2009 Nov 11).

- While screening cells for genes involved in muscle cell fusion, Dr. Grace Pavlath and her research team found that the gene for odorant receptor MOR23 was upregulated as migrating cells were beginning to fuse and form muscle fibers. After confirming that the gene produced the MOR23 receptor protein, the investigators proceeded to dissect the cell biological function of MOR23 in muscle cell growth and repair. Decreased expression of MOR23 produced more, but smaller, muscle fibers; increased expression of MOR23 generated fewer, larger, muscle fibers. The smaller fibers in the muscle with decreased

MOR23 expression were due to myofiber branching, an unexplained phenomenon seen in injured, aged, or diseased muscle (*Dev Cell.* 2009 Nov;17(5):649-661).

- Drs. Ellen Lumpkin and Stephen Maricich and colleagues examined a mouse model that did not express the gene *Atoh1* in most regions of the skin—a gene that is essential for Merkel cell development. Although the structures for touch-sensing in these mice were mostly intact and normal, they lacked Merkel cells. The sensory neurons of the mice did not respond to light touch, indicating that Merkel cells are critical for light touch sensation, and neurons that normally signal in response to light touch do not respond in the absence of Merkel cells. Further studies with this *Atoh1* knock-out mouse also revealed that Merkel cells originate from skin precursor cells, rather than the neural crest cells of embryonic tissue from an earlier stage of development (*Dev Biol.* 2009 Dec 1;336(1):76-83. Epub 2009 Sep 25; *Science*. 2009 Jun 19;324(5934):1580-1582).

- Two independent research groups used different approaches to identify Early Growth Response-1 (EGR-1) as a key molecular regulator of gene expression in the signaling pathways involved in fibrosis. The research teams led by Dr. Carol Feghali-Bostwick and Dr. John Varga were able to control the fibrotic responses of cells by increasing or decreasing levels of EGR-1 (*Am J Pathol.* 2009 Aug; 175:605-615; *Am J Pathol.* 2009 Aug; 175:1041-55).

- A multi-institutional research team led by Drs. Diane Mathis and Christophe Benoist compared the components of immune complexes found in joints of patients with rheumatoid arthritis (RA) and osteoarthritis (OA). Findings suggest that autoantibodies directed against molecules deposited in the joint have the potential to contribute to arthritic inflammation (*Proc Natl Acad Sci USA*. 2009 Sep 15;106(37):15867-15872).

NIH/NIAMS Activities and Plans for the Future

At the time of the last Council meeting, the NIH had just released new guidelines for federally funded studies using human embryonic stem cells and established a registry where it would list the cell lines that researchers can use in NIH-supported projects. In December 2009, NIH Director Dr. Collins approved 40 human embryonic stem cell lines for inclusion in the registry. As of the week prior to this Council meeting, 42 lines were available, and 90 were under review.

Dr. Katz noted that later in the meeting Dr. Collins would provide some insights into his vision for the NIH and his plans for implementing that vision. As the NIAMS Director and as a member of his Scientific Management Review Board (SMRB), Dr. Katz works closely with Dr. Collins. The SMRB is one of several committees advising the NIH Director; Congress established the Board when it passed the NIH Reform Act of 2006. The SMRB is charged with advising HHS and NIH officials on establishing or abolishing Institutes, reorganizing offices within the Office of the Director, and reorganizing Divisions, Centers, or other administrative units within an IC. The SMRB has three working groups which focus in the areas of: (1) Substance Use, Abuse, and Addiction, (2) Deliberating Organizational Change and Effectiveness, and (3) the NIH Clinical Center and Intramural Research Program. Dr. Katz is a

member of the Deliberating Organizational Change and Effectiveness Working Group as well as the NIH Clinical Center and Intramural Research Program Working Group.

Dr. Katz also noted that this meeting would feature a report on the Institute's Intramural Research Program from Drs. John O'Shea (NIAMS Intramural Scientific Director) and Dan Kastner (NIAMS Clinical Director and Director of Translational Research). He reminded Council members that at the time of the last Advisory Council meeting, Dr. O'Shea had just been awarded the 2009 Lee C. Howley Sr. Prize for Arthritis Research, with which the Arthritis Foundation recognizes researchers whose contributions during the previous five years have represented a significant advance in the understanding, treatment, or prevention of arthritis and rheumatic diseases. Dr. O'Shea was recognized for his work on cytokine signal transduction and the roles of Janus kinases and the STAT family of transcription factors in immune cell development and differentiation. In November, Dr. Kastner received the NIH Astute Clinician Lectureship Award, which honors a U.S. scientist who has observed an unusual clinical occurrence and by investigation of this occurrence has opened a new avenue of research.

In September, the NIAMS was in the final stages of awarding many of its ARRA-funded grants. At this meeting, NIAMS Deputy Director Dr. Robert Carter provided Council members with information about how the Institute invested its portion of the funds. Dr. Katz emphasized the need for the Institute to remain informed from Council members about how scientists are using the money to create or preserve jobs, to keep laboratories running, and to advance research.

Dr. Katz noted that Drs. Carter, Joan McGowan (Director of the NIAMS Division of Musculoskeletal Diseases), and Serrate-Sztein would be providing Council members with an update on the NIAMS' efforts to support extramural clinical research. He thanked Dr. O'Keefe, Ms. Pickford, and Mr. Stephenson for attending the recent NIAMS scientific roundtables held to solicit input from a broader community. Clinical researchers, physicians, and patient advocates from across the country participated in these discussions. Dr. Katz noted that the meeting also would feature a presentation on NIH's plans for the next phase of the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative.

As a result of discussions that have involved many Council members, the Institute has made decisions on a few operational changes, such as requiring planning grants before supporting a full clinical trial, and funding clinical trials as cooperative agreements rather than through a standard R01 grant mechanism.

The topic of registries as a conduit to clinical trial recruitment was raised at several of the recent NIAMS roundtables; this issue is shared by researchers supported by other ICs. To better pair researchers and volunteers, member institutions of the NIH's Clinical and Translational Science Award (CTSA) Network recently established a registry called ResearchMatch.org. Through the Web site, which has been operating since November, ResearchMatch will connect any interested individual residing in the United States with researchers who are approved to recruit potential research volunteers through the system. At present, only researchers affiliated with participating CTSA institutions are eligible to use ResearchMatch. However, plans are in place to make ResearchMatch available beyond the CTSA consortium by 2011.

NIH's partnership with NASA to encourage biomedical research on the International Space Station continues to generate considerable interest, both from within the scientific community and on Capitol Hill. Dr. Katz applauded Dr. McGowan's efforts to generate interest on the part of other ICs in trying to identify utilization of the station in terms of earth science. A program announcement has been released, with nine ICs participating. Last month, Dr. Katz presented on "Science and Human Space Flight Today" at a Symposium on Human Space Flight and the Future of Space Science, sponsored by the Universities Space Research Association and George Washington University's Space Policy Institute. In October, the Senate Commerce, Science, and Transportation Subcommittee on Science and Space held a hearing entitled, "The Case for Space: Examining the Value." Dr. Katz's testimony addressed biomedical research advances and opportunities that are available through the International Space Station.

Dr. Katz explained that the Institute continues to work with the NIAMS Coalition to share the latest research advances and related developments. The second Coalition Outreach and Education Meeting was held on November 3, 2009, with the goal of providing Coalition members with an opportunity to network and share best practices on the importance of connecting science to the public. As the keynote speaker, the Honorable John Edward Porter, former U.S. Representative and current chair of Research!America, emphasized the importance of building bridges between the public and the scientific community.

Dr. Katz reported that the NIAMS Web site ranked highly in a recent American Customer Satisfaction Index poll; in fact, the site scored better than a number of popular commercial Web sites. He acknowledged the efforts of NIAMS OCPL staff and the NIAMS Web team for ensuring that the Institute's site provides up-to-date and relevant information to the American people.

Council members were provided with a number of information dissemination pieces, including:

- An English/Spanish bilingual booklet explaining joint replacement surgery and a 2010 pocket planner, both produced by the NIAMS OCPL and distributed through the NIAMS Information Clearinghouse.

- The cover article of the most recent issue of the *NIH News in Health*, in which Dr. Joan McGowan discusses osteoporosis.

- The October 2009 issue of the *NIH Catalyst*, which describes work from the laboratory of NIAMS intramural investigator Dr. Richard Siegel and highlights Dr. Raphaela Goldbach-Mansky's ground-breaking work on the pediatric autoinflammatory disease deficiency of the interleukin-1 receptor antagonist (DIRA) at the NIH Clinical Center.

Discussion

Council member Dr. Kathleen Green, Joseph L. Mayberry Professor in the Department of Pathology/Cancer Center at Northwestern University Medical School, asked if there is an online resource that can be used to view and submit information on the use of ARRA funds. Dr. Katz indicated that this is the case and would be discussed in more detail by Dr. Carter later in the meeting. Dr. Katz explained that both the human and science perspectives with regard to the use of ARRA funds are being solicited. Dr. Green suggested that writing letters to the editors of local newspapers may be another approach to publicizing these efforts.

V. HIGHLIGHTS OF FY09 NIAMS AMERICAN RECOVERY AND REINVESTMENT ACT ACTIVITIES

Dr. Carter provided an in-depth view of the NIAMS ARRA budget and the science it is funding. He presented a slide showing ARRA funding for both NIAMS and NIH overall for FY 2009; and he noted that supplements were entirely paid in FY 2009, which is not the case for the other ARRA-related mechanisms. Dr. Carter commented that in all of the ARRA-related mechanisms, NIAMS investigators performed very well in terms of submitting proposals that crossed boundaries such that they were appropriate for trans-NIH funding; these were supported by the NIH Office of the Director and will be administered by the NIAMS.

As of January 2010, the total NIAMS ARRA allocation was $132.7 million. The leading mechanisms funded were Grand Opportunities (or RC2s, $41.75 million), R01s ($19.7 million), RPG-revision-competing supplements ($17.5 million), and Challenge Grants ($15.5 million). Dr. Carter noted that the payline extension across existing NIAMS mechanisms is substantial, but less than many ICs; this allows the Institute to continue funding large initiatives in areas of emphasis.

Dr. Carter then provided an overview of projects funded through the ARRA program, highlighting ARRA investment reports on diverse research efforts NIAMS has supported. He noted that the Institute selected applications to fund that likely would not be funded through usual operations. Areas of emphasis included: regenerative medicine in musculoskeletal and skin diseases; wound healing, management, and infection prevention; pediatric rheumatic and skin diseases; autoimmune rheumatic and skin diseases; muscular dystrophy; osteoarthritis; and osteoporosis and fracture healing. Within each of these areas of emphasis, Dr. Carter listed some of the topics with specific projects as follows, which demonstrate the breadth of projects funded by NIAMS using ARRA funds:

- Regenerative Medicine
  - Biomaterials: muscle scaffolds, cell signals in graft and integration, multi-polymer scaffolds, engineering and meniscus.
  - Cellular: pressure and fibrocartilage stem cells, biophysical signals in bone stem cells, mechanical stimulation in bone repair, large animal model of cartilage regeneration, regulation of skin-derived induced pluripotent stem cells.

- Skin, Scars, and Barrier Function
  - Wound Healing: cell sprayer, engineering, porous barrier, basonuclin, skin stem cell.
  - Burns and Scars: burn progression, restoration, hypoxic.

- Pediatric Disease
  - Juvenile Idiopathic Arthritis (JIA): Childhood Arthritis and Rheumatology Research Alliance – comparative effectiveness research (CER), genetics of JIA.
  - Hemangiomas: severity scale.

- Autoimmunity
  - Mechanisms: genetics and gene expression in psoriasis, psoriatic arthritis, and lupus; T cells - Th transcriptome and role of intestinal flora; physiology - neuroimmunology and atherosclerosis.
  - Treatment: CER – rheumatoid arthritis and psoriasis, zeta chain-associated protein kinase 70 as target, biorepository for pharmacogenetics in rheumatoid arthritis.
  - Disease Monitoring: biomarkers in rheumatoid arthritis, lupus, and vasculitis.

- Muscle Disease
  - Muscle Biology: regulation of differentiation, myotome formation.
  - Mechanisms of Muscle Disease: iPS for facioscapulohumeral muscular dystrophy, protein binding to RNA, neuronal nitric oxide synthase in Duchenne muscular dystrophy.
  - Therapies: models, molecules, gene-based, monitoring.

- Osteoarthritis
  - Detection and Biomarkers: magnetic resonance imaging, genetics, blood and urine (and messenger RNA).
  - Treatments: treatment for post-traumatic and early osteoarthritis; genetics of mouse models; biomechanics, tissues, and healing; large animal models; tissue banking.

- Bone and Fracture
  - Structure, Risk, and Genetics: in complex diseases, bone marrow fat, genetics with existing data sets, genetics of sex differences.
  - Bone Development: molecular and cellular responses to loading and exercise, methodology, role of maternal diet.
  - Fracture Repair: nanocomposite cement, aging and treatment.

Dr. Carter also reported on ARRA investments in the NIAMS IRP. ARRA funds were used to purchase an advanced fluorescence lifetime imaging microscope for visualizing cells or molecules. ARRA funds also were used to purchase a genome analyzer for large-scale DNA and high-throughput processing.

There are a number of ARRA initiatives still open at the Institute, including the NIH Basic Behavioral and Social Science Opportunity Network (OppNet), the NIH Director's Opportunity for Research in Five Thematic Areas, and the summer supplements.

Dr. Carter emphasized the Institute's desire to receive feedback on ARRA-related success stories – stories that resonate with ARRA goals to stimulate the economy, create and preserve jobs, and advance biomedical research. Of particular interest is information on jobs retained or created; the enhancement of projects by allowing new efficiencies, new directions, or additional resources; the expansion of research teams through new personnel or collaborations; and large and small, immediate and long-term effects. These success stories can be viewed online at www.niams.nih.gov/recovery. Council members were asked to encourage their peers to submit any relevant information to the Institute.

Discussion

Dr. Katz reminded Council members that the projects described by Dr. Carter were made possible by the $132 million in ARRA funding, for which the Institute is extremely grateful. Council member Dr. Cliff Rosen, Director of Translational Research at Maine Medical Center, noted that his organization recently hosted its representative from the 1st Congressional District and her administrative group; this was extremely valuable visit for them to see how recovery money was being applied. He suggested that this may be an effective way to reintroduce congressional delegates to this concept.

Dr. Branden Brough, Legislative Liaison in the NIAMS Office of Science Policy and Planning, explained that Office staff sent summaries for each of the ARRA investment reports to the individual congressional offices that had an RC1 or RC2 grant in their district or state to explain what researchers were doing with the allocated ARRA funds. A total of 77 different congressional offices were contacted.

Council member Dr. Betty Diamond, Chief of the Laboratory of Autoimmune Diseases at the Feinstein Institute of Medical Research and Professor at Albert Einstein College of Medicine, noted that many ARRA-funded activities could potentially extend beyond two years. She asked about plans to possibly extend these projects. Dr. Katz noted that it was made clear to applicants and reviewers that these projects were to be completed within two years. The NIAMS has not made any commitment for FY 2011 funds other than a very small amount of money for a third year of R03 applications which were paid beyond the usual payline. In terms of the science, if these ARRA-supported projects are competitive in the future, it would demonstrate further success.

Dr. Rosen suggested that slides with information on ARRA-specific projects and areas of emphasis could be provided to researchers who participate in these studies for presentations at national meetings to promote the visibility of these activities. Dr. Katz agreed that this was an excellent idea and that the NIAMS OCPL will implement this task.

VI. NIAMS INTRAMURAL RESEARCH PROGRAM REPORT

Dr. O'Shea explained that the NIAMS IRP includes approximately 250 staff, comprising scientists, physicians, nurses, trainees, and administrative/support staff. The IRP has about 20 faculty members, including Principal Investigators, tenure-track and tenured investigators,

adjunct investigators, and staff scientists. The program features core facilities and a training and career development section. Dr. O'Shea highlighted some of the IRP researchers and their areas of interest, noting that the IRP relies heavily on the Institute's Board of Scientific Counselors to rigorously review and guide the program's activities and ensure that the best science is being conducted.

Dr. O'Shea discussed NIAMS IRP efforts related to epigenetic regulation; through ARRA funding, IRP researchers received a Director's Challenge Award for a trans-NIH project in epigenetics as part of a multi-institutional effort that includes researchers from the National Heart, Lung, and Blood Institute, the National Cancer Institute, and the National Eye Institute. Based on external cues, cells eventually become muscle cells, skin cells, lymphocytes, etc. All cells have the same DNA, but they have the ability to recall when they differentiate that they are muscle cells, skin cells, etc. This epigenetic landscape relates to gene expression and alterations in chromatin structure. Although DNA is commonly thought of as being a simple three-billion base pair stretch, in reality, there are many complexities inherent in DNA structure. DNA is wrapped around histones, which compact the DNA or allow for access to transcription factors. In addition, inter- and intrachromosomal interactions and intermolecular interactions make this even more of a dynamic process. Histones can be modified in an immensely large number of ways, and all of this complexity in structure and modifications influences how genes are expressed.

Investigators in the NIAMS IRP have utilized the genome analyzer purchased with ARRA funds in a number of cutting-edge projects. Dr. Vittorio Sartorelli, Senior Investigator in the Laboratory of Muscle Stem Cells and Gene Regulation, has been studying how polycomb proteins regulate muscle stem cells. By using the genome analyzer to analyze micro RNA expression, Dr. Sartorelli has found that there are micro RNAs that regulate polycomb proteins and determine whether a cell is differentiated or in its pleuripotent state.

Dr. Rafael Casellas, Investigator in the Laboratory of Molecular Genetics, is using the genome analyzer to survey the expression of micro RNA in all tissues. He has identified many new micro RNAs and begun examining their expression. Specifically, Dr. Casellas has identified expression of some micro RNAs that are high in some B cells and determined that some micro RNAs appear at different stages of B cell development. The expression of these micro RNAs can be related to the epigenetic modifications.

Dr. O'Shea noted that T cells also differentiate, which has important implications for host defense against infection and for autoimmune disease. For reasons not fully understood, they also drive conditions such as allergies and asthma. Dr. O'Shea is using the genome analyzer to gain a more profound understanding of the role of STAT3 protein in Job's syndrome, a primary immunodeficiency disease. STAT3 has multiple functions in regulating the cytokine IL-17 and binds to other transcription factors important in Th17 differentiation. Patients with this disorder do not develop Th17 cells, which explains why they are unable to fight infection.

One factor complicating the benefits of the genome analyzer is that it produces an overwhelming amount of data. The NIAMS Board of Scientific Counselors has encouraged the IRP to enhance its systems biology and bioinformatics capabilities. Three new staff members have been

recruited to assist in these activities. In the future, it is likely that the IRP will recruit a tenure-track researcher in systems biology.

Dr. Kastner described some of the ongoing activities on the clinical side of the IRP. Drs. Raphaela Goldbach-Mansky, a tenure-track investigator in the Office of the Clinical Director and Ivona Aksentijevic, a staff scientist in the Genetics and Genomics Branch, have described DIRA, a new autoinflammatory disease. A patient was referred to Dr. Goldbach-Mansky with a constellation of symptoms similar to those associated with neonatal-onset multisystem inflammatory disease (NOMID). NOMID was ruled out as a diagnosis for this patient, who was treated with the IL-1 receptor antagonist anakinra, and there was a dramatic effect within the course of a week. Drs. Goldbach-Mansky and Aksentijevic found that the patient was homozygous for a two base-pair deletion in the IL-1 receptor antagonist gene (a founder effect seen in the island population of Newfoundland, where this patient was born). Mutations in this gene among patients with the same or similar phenotype have been seen in other populations as well (e.g., Dutch Americans).

In another patient presenting with NOMID-like symptoms who only partially responded to anakinra therapy, Dr. Goldbach-Mansky and colleagues conducted a genome-wide SNP analysis and found that the patient had a 175 kb deletion of the relevant region of chromosome 2 that includes the IL-1 receptor antagonist gene and five other genes in the IL-1 family. This finding explained why the patient was only partially responsive to anakinra and the condition has been identified as variant DIRA.

Dr. Kastner discussed genome-wide associated studies related to Behcet's disease, a disease common in the Middle and Far East characterized by inflammation of the mouth, ocular inflammation, and genital lesions. Behcet's disease has a familial component to it, although it is not a Mendelian disease like DIRA. NIAMS IRP investigators established a collaboration with researchers in Istanbul, Turkey, in which genome-wide SNP analyses were carried out on 1,332 Turkish control individuals and 1,329 patients with Behcet's disease. A variant leading to decreased production of IL-10 (an anti-inflammatory cytokine) was found to have genome-wide significance.

Dr. Kastner noted that NIAMS IRP investigators are continuing their collaboration with Dr. Peter Gregersen of the North American Rheumatoid Arthritis Consortium; he pointed out a number of rheumatoid arthritis susceptibility genes that have been identified through that collaboration.

Dr. Michael Ward, an investigator in the Office of the Clinical Director, has been involved in genome-wide association studies of ankylosing spondylitis, and has identified new susceptibility alleles associated with the disorder, including the decoy receptor for IL-1 and an anthrax toxin receptor. Dr. Ward also has been involved in outcomes research focusing on ankylosing spondylitis and in advanced imaging studies trying to use computed tomography and magnetic resonance to identify the volume of new bone formation in these patients.

Dr. Robert Colbert, a pediatric rheumatologist in the Office of the Clinical Director, has been studying pediatric spondyloarthropathy. He has developed the novel concept that the HLA-B27

association may be due to misfolding of the HLA-B27 protein, which leads to increased production of IL-23 by innate immune cells. Dr. Colbert has also been working on gene expression profiling in pediatric arthritis.

Dr. Kastner briefly described other ongoing noteworthy initiatives within the NIAMS IRP, including the Center for Human Immunology, Autoimmunity, and Inflammation; the Henry Metzger and Lawrence Shulman Scholars Program; partnerships with Johns Hopkins and DuPont Hospital for Children; and development of protocol service centers to help investigators write their protocols. He noted that the number of tenure-track investigators who are writing protocols is increasing dramatically, in large part because of an Institute commitment to this process. This has contributed to an increased utilization of the NIH Clinical Center.

In terms of future directions, the NIAMS IRP efforts will include: (1) expanding clinical studies of Bechet's disease, including targeted therapies; (2) conducting genome-wide association studies on systemic JIA; (3) next-generation sequencing in mutation-negative autoinflammatory patients; (4) expanded natural history studies of spondyloarthropathy in children and adults; (5) continuing the assistant clinical investigator program; and (6) new recruitments for senior faculty.

Discussion

Dr. Katz thanked Drs. O'Shea and Kastner for their presentations and efforts within the NIAMS IRP. He noted that Council members were provided with a recently published booklet discussing the opportunities for research at the NIH; many areas of interest to the NIAMS are featured in the booklet.

Council member Dr. Henry Kronenberg, Chief of the Endocrine Unit at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School, noted that the NIAMS does not include basic bone biology as a part of its IRP. The National Institute of Dental and Craniofacial Research is the only NIH IC that has a bone intramural program. He suggested that it is the responsibility of the NIAMS IRP to recruit an expert in bone to benefit the bone and inflammation/autoimmune communities. Dr. Katz commented that at present, the bone biology community is well served by critical masses around the country of excellent investigators. If more resources become available, the Institute may decide to create a true bone biology program within the NIAMS IRP. Dr. Katz emphasized that bone issues are a priority for the Institute, but given the reality of budget constraints and other NIAMS priorities, NIAMS leadership have not felt it appropriate to institute such a program at present.

VII. CLINICAL TRIAL ROUNDTABLES

Dr. Carter discussed the recent history and evolution on the NIAMS' thinking about clinical trials. He explained that the Institute's goal in terms of its clinical trials is to, within the available resources, support trials that are timely, informative, and improve clinical outcomes. In December 2008, the NIAMS' clinical trials portfolio was reviewed, and this review was discussed during a NIAMS Scientific Retreat session in April 2009. In June 2009, the portfolio was presented to and discussed by Council members. In September of that year, the Council was presented with proposed FY 2011 initiatives, including the concept of using the Clinical Trials Planning Grant (U34) as a necessary first step for all clinical trials. During November and December of 2009, five roundtables were convened in the areas of rheumatic diseases, skin diseases, bone diseases, muscle diseases, and orthopaedics and osteoarthritis. Key questions guiding the discussions at these roundtables were: (1) What are the current clinical needs and opportunities? and (2) How can the NIAMS identify the opportunities for clinical trials with the greatest impact?

Dr. Carter described the key themes and take-away messages from each of those roundtables, as follows:

- Rheumatic Diseases:
  - Clinical questions include who to treat and with what, when to stop, and how to treat limited disease.
  - The field has multiple effective therapies, but little comparative effectiveness research.
  - Lethal diseases and comorbidities remain challenges.
  - Research networks build efficiencies in the conduct of clinical trials.
  - Databases and biorepositories are needed to understand chronic diseases.

- Skin Diseases:
  - There are documented effective therapies only in acne and psoriasis; there is still a need for target identification and effectiveness studies.
  - Treatments and practice-based comparative effectiveness research is needed for wound healing, fibrosis, itch, and skin cancer (and many specific diseases).
  - Approved drugs for common diseases can be tested in rare diseases.
  - Validated outcome measures and networks are needed.

- Bone Diseases:
  - Further research is needed to better understand whom to treat, with what medication, and for how long.
  - Risk identification (risk of fall versus risk of fracture).
  - Examine how best to treat patients with comorbid conditions.
  - Existing datasets can identify opportunities for high-impact clinical trials.
  - There is a need to expand anabolic treatment to prevent bone loss and restore bone.
  - Patient preference and communication need to be considered as clinical trials issues.

- Muscle Diseases:
  - Networks are in place, but patient-oriented, validated outcome measures and standardization of best practices across centers are needed for clinical trial design.
  - More basic science of muscle is needed to provide the foundation for future translational research.
  - Improved patient care in centers will help solve the challenge of patient recruitment.
  - A way to link improved diagnostic criteria with genotype.
  - Proof of concept includes first-in-human and is required prior to an investment by industry.

- Osteoarthritis and Orthopaedics:
  - Data on primary prevention, including sports injury, joint injury in the elderly, and weight loss are needed.
  - Validated surrogate end points are needed.
  - Primary care providers can contribute to clinical studies on interventions for patients who have musculoskeletal pain.
  - The ability to recruit patients may be the most meaningful indicator of a successful clinical trial.
  - Systematic reviews by professional societies have identified practice areas with little evidence for effectiveness.

Dr. Serrate-Sztein noted that one of the primary messages generated at the roundtables is the fact that there is great heterogeneity in terms of the level of expertise and experience with the different diseases across the different communities, each of which has unique needs. Dr. Katz added that there was a clear collective identification of the need for networks by almost every group represented at the roundtables. Networks can be very effective and beneficial, but there are limits imposed by budgetary considerations.

Dr. Carter noted that there were three additional common themes that arose during the roundtable discussions: (1) remain open to investigator-initiated proposals for clinical trials; (2) solicit advice from community representatives to help identify the most critical clinical needs and opportunities; and (3) there is a need for an ongoing mechanism to solicit input as to clinical needs and opportunities from multiple stakeholders, including patients and non-academic clinicians.

Dr. Carter described a proposed model for how best to address the first two themes. For investigator-initiated clinical trial applications, the first step is that the investigator is required to submit a request to submit a planning grant (i.e., a letter of intent, précis, outline of study, budget estimate) that will be considered by a subcommittee of the NIAMS Advisory Council, which can call in *ad hoc* expertise as needed. The subcommittee of the Advisory Council would provide feedback to NIAMS leadership as to whether the planning grant for the trial is a high priority or not, and NIAMS leadership then responds to the investigator as to whether their request is accepted or not. Importantly, the screen in terms of whether the Institute is interested in the clinical trial occurs at this point, not later in the process.

Once an investigator submits a planning grant proposal, it undergoes review through a NIAMS-convened study section with the appropriate expertise, is scored, and then considered for support. Within the planning grant are a number of milestones; if those milestones are met and there are no outside changes (e.g., changes to the NIAMS budget), the NIAMS will accept an application for a U01, which will undergo peer review at that time. As part of this proposed model, the clinical trial planning grant becomes an integrated part of the clinical trial itself, and there is a decision made up front to determine whether it is a high-priority area for the Institute.

Dr. Carter explained that the subcommittee of the Council would include Council members as well as *ad hoc* members on an as-needed basis to provide additional expertise. It is anticipated that the subcommittee would meet once or twice per year (possibly aligned with Council meetings) and that subcommittee members would serve two-year terms that overlap with their Council tenure. Activities of the subcommittee would be overseen by the NIAMS Deputy Director. The group's charge would be to provide recommendations to NIAMS leadership to inform the decision making process.

Dr. Carter then addressed the identified need for an ongoing mechanism for soliciting input as to clinical needs and opportunities from multiple stakeholders, including patients and non-academic clinicians. NIAMS Program Directors currently receive input from a number of sources (e.g., scientific organizations, voluntary health organizations, NIH and HHS priorities, NIAMS Scientific Retreats, scientific publications, interactions with applicants and grantees). To formalize ongoing input from the community, Dr. Carter presented a proposed model for obtaining community input for clinical trials. Program staff can use small group meetings, as needed, to obtain advice from the community. The Institute could also issue requests for information to inform program staff. These inputs, along with information obtained through the approaches already in use, would be organized and submitted to NIAMS leadership for consideration by program staff. NIAMS leadership, in turn, would turn these over to the aforementioned subcommittee of the Advisory Council and then the larger Council overall, which would provide advice back to NIAMS leadership on which types of solicitations should be issued by the Institute. Dr. Carter acknowledged that this model is a work in progress and that more thought is needed as to how NIAMS program staff would organize and analyze the different types of inputs. In addition, the mechanism and amount of funding has yet to be determined.

Dr. Carter explained that the overall goal is to help better inform the decision making process. With regard to the selection of clinical trials, the different factors influencing decision making include the cost of the project, the likelihood of significant benefit, monetary cost of disease, prevalence, etc. He closed his comments by summarizing that the Institute is trying to balance these considerations when determining which clinical trials to fund, hoping to set up a process that features the most informed decision making, with input from Council, to more firmly establish how the NIAMS solicits investigator-initiated proposals and how it considers proposals from the community.

Dr. McGowan explained that at present, most of the clinical trials funded by the Institute come to the NIAMS as investigator-initiated R01 grant applications. A few are multicenter trials, but for the most part they are small, single-center trials. Applicants must obtain agreement from the

NIAMS when submitting applications of more than $500,000 per year. Those are considered specifically and individually before they are accepted. A large number of applications are coming to the institute at just under the $500,000 per year level and are reviewed by the Center for Scientific Review (CSR). Oftentimes investigators have a tremendous amount of work to do before the trial is implemented; the NIAMS believes that through collaboration with the investigator and other communities, it can be helpful to investigators in this regard and can be better stewards of limited clinical trials dollars. The intent of the proposed models is to provide tools for investigators and the Institute to get **timely**, significant, and potentially health-changing trials into the literature and into health care. Dr. Serrate-Sztein noted that it is hoped that this type of system, utilizing significant input from the community, will also allow for greater transparency.

Dr. Katz added that it is important for the NIAMS to be informed of the possibilities for conducting comparative effectiveness research. These types of exercises are intended to inform the Institute and help it prioritize.

Discussion

Dr. Kastner commented that input to the Institute has to be submitted in a timely, efficient manner, because the NIAMS is working on diseases from which people are suffering. Dr. Katz explained that the two-year planning grant has been proposed based on the Institute's experience—once the NIAMS commits to funding a clinical trial, it typically takes almost two years to enroll the first patient. Dr. McGowan added that the planning grant is for up to two years; it is expected that most clinical trials will only take one year of planning. The planning grant is intended to provide investigators with the appropriate amount of time to develop and implement a trial.

Dr. Serrate-Sztein commented that from the point of view of the investigator, it is a long time between the point at which a clinical trial is accepted and the time the first patient is enrolled. Once the idea for a clinical trial is in place and review has occurred, investigators have been able to use the planning grant period to prepare. She emphasized that the Institute is not intending for every trial to require a two-year planning phase. Some researchers will need more time than others to identify potential trial-related issues. Dr. Serrate-Sztein also noted that by having more applications reviewed within the NIAMS, it may shorten the time between application submission and award.

Dr. Henry Kronenberg commented that implementing this type of planning grant system gives some much-needed flexibility to the process. The concept of establishing a separate group of peers who are experts in clinical trials is important as well. Dr. Kronenberg also suggested that there are some fundamental problems associated with the proposed models. He cautioned that the extramural community may view these programs as a way for NIAMS program leadership to take complete control of clinical trials and put themselves between scientists and the investigators' peers who are evaluating the science. NIAMS leadership has an important role in facilitating the interactions between scientists who are submitting applications and other scientists from the extramural community who are reviewing their applications. There is strength in the study section at CSR, and the NIH is correct in having it serve as the bedrock of

how clinical science is conducted. Dr. Kronenberg suggested that the Institute modify the proposed model by establishing a study section in lieu of the subcommittee of the Advisory Council. This study section would be different than a traditional study section in that it would meet more frequently (monthly or every two or three months), receive the requests to submit planning grants (including the précis, budget, etc.), and would decide—with the help and advice of NIAMS program staff—which of these investigator-initiated ideas is worthy of being submitted as a planning grant. Dr. Kronenberg cautioned against giving up the direct interface between clinical scientists and peer review study section experts from the beginning to the end in terms of making decisions about the priority grant submissions. In a way, he said, his suggestion protects NIAMS program staff, who would still be heavily involved.

Dr. Diamond commented that other ICs have processes in place similar to the models presented by Dr. Carter. She expressed enthusiasm for Dr. Kronenberg's suggestion to have a study section devoted to these applications and explained that it may provide the Institute with the opportunity to bring in outside experts earlier in the process. She suggested a rotating core of experts external to the NIAMS serve on the study section proposed by Dr. Kronenberg, keeping everything else in place as presented by Dr. Carter.

Dr. O'Keefe commented that the portfolio of clinical research is relatively small and emphasizes the need for careful oversight and management to ensure that the goal of improving public health across communities is met.

Dr. Rosen explained that there is not always sufficient expertise to review clinical trial grant applications in typical study sections. He suggested that if this model is presented in such a way that it is viewed as assistance, rather than a barrier, to the investigator, it will open new avenues for making clinical trials more efficient and effective in terms of reaching its end. Many trials reviewed by clinical investigators in study sections have had to be redesigned or stopped because the endpoints were not sufficient. Because of their complexity, study sections reviewing clinical trials require expertise above and beyond what is found on a typical study section.

Dr. Carter explained that the intention of the model presented for investigator-initiated proposals was to move the decision on whether to accept the proposal to a point much earlier in the process. This would especially be useful in helping to screen whether large, expensive projects should go forward at the expense of a number of smaller, less expensive projects. He suggested that the group currently proposed as a subcommittee of the Council could evolve to take a form similar to the modified study section proposed by Dr. Kronenberg. Dr. Katz commented that the NIAMS currently accepts R34 applications in areas it may not ultimately support. The model proposed by Dr. Carter moves the decision making component to a much earlier stage and would prevent these situations. He emphasized that NIAMS leadership will not be removed from this process.

Council member Dr. Crofford, Chief of the Division of Rheumatology in the Department of Internal Medicine at the University of Kentucky, complimented NIAMS staff for their efforts in this area. She expressed concerns similar to those voiced by Dr. Kronenberg and suggested that it be made more clear that peer review, if not a study section, plays a more visible role. From an extramural standpoint, one would not want to see a purely institute-related filter determining

which applications pass through. Dr. Crofford suggested including a standing review group that represents more than a subcommittee of the Council, a clinical trials program advisory council that would be a standing body beyond a subcommittee of the Council.

Dr. Diamond commented that the point of the model is to have a filter that allows the Institute to make decisions on whether to accept an application, based on need, priorities, budget, etc., early in the process. She suggested that this filter function should be carried out by NIAMS leadership rather than a subcommittee. The end result should be a model that does not allow the submission process to stop with NIAMS leadership without any extramural input. She asked about where opportunities to partner with other ICs appear in the process. Dr. Katz indicated that these opportunities sometimes are obvious and present themselves early in the process; other times these opportunities arise later. The proposed model does not eliminate these partnerships, and the Institute is committed to identifying these collaborative opportunities as early as possible. Dr. Kronenberg indicated that the modifications suggested by his fellow Council members would address his concerns. He noted that there is a difference between a subcommittee of the Council with occasional participation from *ad hoc* experts and a larger group that would be constituted as an extramural advisory board—such a group represents a more feasible version of his earlier suggestion to utilize a modified study section. He urged a more obvious and explicit ongoing incorporation of the extramural community into the process. Dr. Katz noted that the difficulty in having a standing committee is that it would be impossible for that group to include all of the expertise required, given the breadth of areas of interest to the NIAMS. Dr. Kronenberg suggested that having a large group of *ad hoc* experts available would be beneficial, noting that the identities of those experts should be available and visible.

VIII. NEW VISION FOR NIH

NIH Director Dr. Francis Collins noted that the NIAMS is engaged in a host of interesting basic and clinical applications, and he expressed enthusiasm for presenting to the Council some of the exceptional opportunities facing the NIAMS and NIH overall.

Dr. Collins published a paper in the January 1, 2010, issue of *Science* that put forward the following five exceptionally appealing opportunities for future NIH investment:

- Applying high-throughput technologies to understand fundamental biology and to uncover the causes of specific diseases.

- Translating basic science discoveries into new and better treatments and having academic investigators empowered to play a stronger role.

- Putting science to work for the benefit of health care reform. Continue comparative effectiveness research, understanding health behaviors, health economics, etc.

- Encouraging a greater focus on global health, particularly in terms of infectious and non-infectious causes of morbidity and mortality across the globe.

- Reinvigorating and empowering the biomedical research community and encouraging young investigators.

Dr. Collins reminded Council members that the President's budget for FY 2011 was released on the day before this meeting and that the NIH would receive an increase of 3.2 percent under this budget. He commented that the NIH likely would not have been given this proposed increase had it not been for its ability to make the case for exceptional scientific opportunities. He presented a slide illustrating how the FY 2010 NIH budget is being allocated. Approximately 84 percent of the budget funds extramural activities (of extramural funds, about 53 percent is used to fund RPGs). Dr. Collins noted that ARRA dollars are coming to an end in 2010, and so the total funding for the NIH will take a significant downward turn.

Advancing knowledge through basic research is a fundamental component of NIH's mission. Dr. Collins assured Council members that this will continue to be a driving force for the NIH. The major way in which the NIH will continue to make advances will be on the basis of individual investigators with creative ideas. Dr. Collins referred to the work of Dr. Marshall Nirenberg, who was a Principal Investigator in the Laboratory of Biochemical Genetics at the National Heart, Lung, and Blood Institute, as an example of the type of investigator the NIH must make sure it is supporting. Dr. Collins noted with sadness that Dr. Nirenberg passed away in January this year. Dr. Nirenberg developed evidence of the genetic code on the NIH Campus, and he was one of 131 NIH-supported Nobel Prize winners.

Dr. Collins discussed basic science that has clinical implications, using the rare, debilitating autoinflammatory disease NOMID as an example. Basic science findings suggested that the disorder could be treated with anakinra—a good example of how the NIH conducts basic research and then translates and applies the findings.

NIH investments continue to make substantial contributions to public health. For example, the population's longevity has continued to increase by about one year every seven years. Disabilities that might otherwise diminish quality of life have decreased, in large part to NIAMS' efforts. For example, approximately 750,000 Americans suffer from vertebral compression fractures each year, with a direct cost estimated at $12-18 billion annually—a NIAMS-funded study found that the traditional treatment option, vertebroplasty, may be no more effective than placebo.

In addition to benefitting human health, investments in the NIH benefit the economy. Dr. Collins noted that economists have concluded that more than one-half of the economic growth in the United States since World War II has been on the basis of advances in science and technology. Investments made in the NIH, both through base funding and in ARRA funding, are highly warranted. One study suggests that $1 of NIH funding in one year returns $2.21 in saved economic output; very few investments are this impressive. In addition, each NIH grant generates, on average, seven jobs. For these and other reasons, approximately $10 billion in ARRA funding was appropriated directly to the NIH. Of those funds, the large majority ($8.2 billion) was allocated for scientific research. Dr. Collins mentioned a Challenge Grant intended to establish a framework for comparative effectiveness research in pediatric rheumatic diseases. Another Challenge Grant is trying to extend efforts to identify genetic contributors to psoriasis.

He noted that almost all of NIH's ARRA funding has been allocated (or is already encumbered to support the second year of ongoing ARRA grants). ARRA funding has resulted in more than 13,000 grants, 1,085 new investigators (including many new awardees), and an estimated 50,000 jobs created.

He mentioned that President Barack Obama and HHS Secretary Kathleen Sebelius visited the NIH Campus on September 30, 2009, to discuss how science will push forward areas of particular interest, highlight ARRA awards, and reiterate the administration's strong support for science.

With regard to the future, Dr. Collins emphasized the need for the NIH to continue to invest in innovation. The NIH Director's Pioneer Award program is in its fifth year, and has been successful in supporting investigators and allowing them to pursue creative ideas. The program has resulted in a large number of interesting scientific advances. In a similar vein, the NIH New Innovator Award supports a small number of exceptionally creative new investigators who have not previously received a major NIH award. The transformative R01 (TR01) program, which is relatively new, aims to support exceptionally innovative proposals from individuals or collaborative teams. Dr. Collins noted that Council member Dr. Linda Griffith of the Department of Biological and Mechanical Engineering at Massachusetts Institute of Technology received a TR01 award through the National Institute of Biomedical Imaging and Bioengineering for a project to understand how tissues react to various perturbagens in a three-dimensional fashion.

The NIH is funding exceptionally exciting science, but success rates for applicants have been trending downward in recent years (starting with the flattening of the NIH budget in 2003) and currently are at about 20 percent. Dr. Collins noted that because of the exceedingly large number of challenge grant applications received by the NIH, only 4 percent were awarded. Success rates for 2011 will not be known until after the number of grant applications submitted to the NIH is determined; some predictions suggest that there will be a larger-than-average number of applications submitted for FY 2011 funding. Dr. Collins emphasized the need to make the case for NIH by improving and extending outreach, educating others on the importance of biomedical research, inspiring passion for science in the next generation, and fostering innovation. He encouraged Council members to contact the NIH with any suggestions or comments.

Discussion

Dr. Green applauded NIH's efforts with regard to fostering innovation and young investigators, and asked about related NIH-wide efforts at the training level. Dr. Collins explained that NIH's FY 2011 budget includes an increase in funding for training by about six percent (in the previous eight years, the NIH training budget has been essentially flat) through the Ruth L. Kirschstein National Research Service Awards. The NIH has also had numerous discussions about how best to organize its science education efforts and coordinate those with activities at the administration level. The NIH did not have a strong legislative mandate in terms of educating at the level of grades K-12, but does emphasize it as much as possible. Dr. Collins expressed some concern over the growing age of first R01 awardees (currently age 42 years) and expressed hope that there will be an effective approach to decreasing the training period.

Dr. Diamond asked if there is an effort internally within the NIH to consider what level of diversity is needed among R01-supported investigators to maintain a creative enterprise. Dr. Collins acknowledged that this is a complicated issue: what is the ideal workforce in the current climate? Even if the NIH budget could keep up with or exceed inflation, it is unclear what the ideal workforce would look like. It may be that the NIH needs to reconsider how many training slots are needed in the future. Sophisticated modeling will be needed to effectively assess the complexities of such an exercise.

Dr. Rosen noted that the public tends not to trust the government and asked about NIH's long-range plan for reaching out to the public. Dr. Collins agreed that some members of the public have a negative perception of the government and that changing their minds is extremely challenging. It is important to provide information to the public indicating that federally funded biomedical research is a significant contributor to public health. No single method will be effective; a portfolio of approaches is needed. Dr. Collins explained that he recently was appointed as a regular contributor to *Parade Magazine*, which will allow him the opportunity to highlight NIH's work to a wide audience. There is a need for a vigorous communications strategy that is not just reactive, but which also has a proactive plan to disseminate the NIH's message, both at the NIH level and at the individual IC level.

Dr. Kronenberg commented that the NIH is unique in its size and scope and ability to contribute to medical research in this country. He asked if the NIH should have the equivalent of a development office, a vigorous way to identify and encourage the existence of organizations such as the Howard Hughes Medical Institute. Dr. Collins explained that the NIH has played a role in these types of activities on a smaller scale in the past. The NIH has a very solid partnership in place with the Bill and Melinda Gates Foundation.

Dr. John Klippel, President and CEO of the Arthritis Foundation and a member of the Council, asked about the public directly interacting with Dr. Collins, and expressed enthusiasm for the work of the Director's Council of Public Representatives (COPR). He also asked for advice on how advocacy groups can help spread NIH's message. Dr. Collins agreed that COPR serves a very important function at the NIH and noted that efforts are needed to ensure that COPR members are fully engaged. He also indicated that he is very interested in having public input and determining the most effective ways in which to promote biomedical research. He appealed to representatives from professional organizations to provide his office with input on how the NIH message can best be disseminated.

IX. CONCEPT CLEARANCE

The Council was presented with a concept clearance for a research and development contract. Dr. Serrate-Sztein explained that it is a federal requirement that the NIAMS obtain clearance from an advisory board, and the Institute has asked for the Council's input into this process. She further explained that with regard to concept clearance, the Council is asked to advise the Institute regarding the usefulness of the proposed project; it is not being asked to set a priority or make a fiscal decision regarding the concept in question.

Dr. McGowan explained that the concept involves a current contract with the Institute that is managed by Shahnaz Khan, a Clinical Coordinator in the NIAMS DERA. The contract is driven by the need of the Institute to provide some assessment and assistance for NIAMS-funded clinical studies. This mechanism can also be used to provide the Institute with outside expertise if needed. It has also been used to develop the NIAMS' policies and procedures for clinical trials for the benefit of investigators. In addition, the contract has been used to develop educational materials for use by NIAMS staff at scientific meetings. The proposed project was not discussed in detail, only at the concept level; otherwise all participants included in the discussion would have to be excluded from applying. Council members were provided with a brief written summary of the project under consideration for concept clearance.

Discussion

Dr. Rosen asked if the concept differs from current NIAMS activities. Dr. McGowan explained that there is an existing contract in place; the current contract ends next year. Dr. Serrate-Sztein added that the concept is being issued, and the NIAMS is giving consideration to a contract solicitation for an open and full competition as opposed to a sole source award.

Council members voted unanimously in favor of the concept clearance.

X. PROMIS UPDATE

Dr. James Witter, Health Scientist Administrator within the Division of Skin and Rheumatic Diseases, commented that PROMIS continues to be a cutting edge, fast-paced NIH Roadmap initiative. He reminded Council members that the acronym PROMIS stands for Patient-Reported Outcomes Measurement Information System and suggested that the "P" in PROMIS should be broadened to include "persons, people, and participants." PROMIS is a dynamic tool to measure health outcomes from the patient perspective.

Outcomes, from a clinical trial for example, can be reached through objective measures such as x-rays, c-reactive protein measurements, etc.; overall effectiveness/efficacy; adverse experiences; and, from a subjective standpoint, patient-reported outcomes (PROs). Dr. Witter asked Council members to visualize a reliable, easy, and precise instrument able to capture PROs regardless of education, language, race, ethnicity, disability, age, and platform (e.g., telephone, computer, hand-held device). This instrument would have minimal or no cost; be compatible with electronic health records; and could provide instant health status reports to enhance research, improve clinical decision making, and facilitate policy decisions. In the future, with all of this information being collected, it could be analyzed in a meaningful way, resulting in improved patient outcomes. Dr. Witter explained that PROMIS is moving in this direction, although more efforts are needed in terms of tying in with industry.

The PROMIS initiative has been ongoing since 2004 and will be funded through 2013. PROMIS, in essence, leverages the best from the past by collecting items from clinically tested, well-recognized legacy sources in a psychometrically rigorous way. The intent is to utilize

PROMIS to create standards for developing and validating domains and items that constitute those domains. PROMIS will be transparent and understandable, particularly to users (e.g., patients, health care providers). In addition, it will be scientifically defensible from statistical, psychometric, and clinical perspectives and will allow adaptability and continuing relevance. Dr. Witter highlighted two of the starting objectives tied to the PROMIS initiative: (1) create item banks using modern measurement theory, and (2) plan for a public-private partnership.

The first funding phase (2004-2009) included psychometric testing and clinical testing. The second phase (2009-2013) includes continued psychometric testing as well as expended clinical testing (with a focus on children, minorities, and patients with disabilities). Dr. Witter described the PROMIS domain development/qualification lifecycle, moving forward from psychometrically-focused testing to clinically-focused testing and clinical care.

Dr. Witter described the PROMIS network structure and noted that there was a robust response to the second funding phase (four RFAs were released), with a total of 15 awards. The PROMIS Statistical Center resides at Northwestern University, as does the Technology Center. The PROMIS Network Center is housed at the American Institute for Research. There are a number of current domain development/early validation projects, including PROs for children and young adults with disabilities, PROs in routine clinical care of patients with HIV, development/validation of PROMIS GI distress, etc. In closing, Dr. Witter referred Council members to the PROMIS Web site, www.nihpromis.org, for additional information.

Discussion

Dr. James Weinstein, Professor and Chair of the Department of Orthopaedics at Dartmouth-Hitchcock Medical Center, asked how PROMIS fits with other work on quality metrics and noted that, particularly given the earlier discussion on clinical trials, these types of tools are very important. He asked how the various ongoing initiatives outside of PROMIS are being coordinated. Dr. Witter explained that work is ongoing to incorporate existing items and ensure nothing is being missed. Dr. Weinstein noted that PROMIS is not always considered in discussions on how to measure health and value, and asked if there is concern that it is getting lost among all of the other initiatives. Dr. Witter acknowledged that there is competition from other projects and that the NIH is doing what it can in terms of outreach and education relative to the PROMIS initiative. Dr. Katz added that PROMIS is currently undergoing a massive validation phase and that the robustness of this tool is only now starting to be seen; it is anticipated that PROMIS will be utilized a great deal in future clinical trials.

XI. COUNCIL SURVEY FOR ENHANCING PEER REVIEW

This portion of the meeting was conducted during closed session.

XII. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 851 applications in closed session requesting $1,016,394,322 and recommended 851 for $1,016,394,322.

XIII. PORTFOLIO PRESENTATION

This presentation was given during closed session.

XIV. ADJOURNMENT

The 70th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 3:00 p.m. Proceedings of the public portion of this meeting are recorded in this summary.

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

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