Department of Health and Human Services
National Institutes of Health (NIH)
Office of the Director (OD)
Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)

Council of Councils Meeting
September 5, 2014

Meeting Minutes

I. WELCOME

James M. Anderson, M.D., Ph.D., Chair of the NIH Council of Councils, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. The meeting began at 8:15 a.m. on Friday, September 5, 2014, in Building 31, Conference Room 6, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson noted that Drs. Carlos D. Bustamante, F. Xavier Castellanos, and Terry Magnuson, as well as Mr. Jeffrey A. Kaufman, were unable to attend the day's meeting. Drs. Richard M. Greenwald and Emery N. Brown participated via teleconference, and Dr. Grace LeMasters participated for the closed session only via teleconference. Dr. Anderson acknowledged that Ms. LaVarne A. Burton, Dr. Castellanos, Dr. Greenwald, Mr. Kaufman, Dr. LeMasters, Dr. K.C. Kent Lloyd, Dr. Joyce A. Mitchell, and Dr. Robert F. Murphy would be rotating off the Council, and he thanked them for their service. The meeting attendees are identified below.

Following introductions and announcements from Franziska B. Grieder, D.V.M., Ph.D., Executive Secretary for the NIH Council of Councils, Dr. Anderson reviewed the day's agenda.

A. Attendance

1) Council Members

Council Members Present

Chair: James M. Anderson, M.D., Ph.D., Director, DPCPSI, OD, NIH
Executive Secretary: Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI
Philip O. Alderson, M.D., Saint Louis University, St. Louis, MO
Marlene Belfort, Ph.D., University of Albany, Albany, NY
Emery N. Brown, M.D., Ph.D., Massachusetts Institute of Technology, Harvard Medical School, Massachusetts General Hospital, Cambridge, MA
LaVarne A. Burton, M.A., American Kidney Fund, Rockville, MD
Janice E. Clements, Ph.D., The Johns Hopkins University School of Medicine, Baltimore, MD
Ana M. Cuervo, M.D., Ph.D., Albert Einstein College of Medicine, Bronx, NY
Steven T. DeKosky, M.D., University of Virginia, Charlottesville, VA
Judy E. Garber, M.D., M.P.H., Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
Lila M. Gierasch, Ph.D., University of Massachusetts, Amherst, MA

Susan F. Goekler, Ph.D., M.C.H.E.S., Directors of Health Promotion and Education, Washington, DC
Richard M. Greenwald, Ph.D., Simbex, iWalk, Thayer School of Engineering, Dartmouth College, Lebanon, NH
Barbara J. Guthrie, R.N., Ph.D., F.A.A.N., Yale University, New Haven, CT
Nancy L. Haigwood, Ph.D., Oregon Health & Science University, Beaverton, OR
King K. Holmes, M.D., Ph.D., University of Washington, Seattle, WA
Norma Sue Kenyon, Ph.D., Wallace H. Coulter Center for Translational Research, University of Miami School of Medicine, Miami, FL
Grace LeMasters, Ph.D., University of Cincinnati College of Medicine, Cincinnati, OH
K.C. Kent Lloyd, D.V.M., Ph.D., University of California, Davis, CA
Craig J. McClain, M.D., University of Louisville School of Medicine, Louisville, KY
Joyce A. Mitchell, Ph.D., F.A.C.M.G., F.A.C.M.I., University of Utah, Salt Lake City, UT
Robert F. Murphy, Ph.D., Carnegie Mellon University, Pittsburgh, PA
Norbert J. Pelc, Sc.D., Stanford University, Stanford, CA
James E. Schwob, M.D., Ph.D., Tufts University School of Medicine, Boston, MA
Gilbert C. White, II, M.D., Blood Research Institute, Blood Center of Wisconsin, Milwaukee, WI

Council Members Absent

Carlos D. Bustamante, Ph.D., Stanford University School of Medicine, Stanford, CA
F. Xavier Castellanos, M.D., New York University School of Medicine, New York, NY
Jeffrey A. Kaufman, M.B.A., Adenoid Cystic Carcinoma Research Foundation, Needham, MA
Terry Magnuson, Ph.D., University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC

2) Liaisons

Janine A. Clayton, M.D., Director, Office of Research on Women's Health, DPCPSI
David M.Murray, Ph.D., Director, Office of Disease Prevention, DPCPSI
G. Stephane Philogene, Ph.D., Deputy Director, Office of Behavioral and Social Sciences Research (OBSSR), DPCPSI (representing OBSSR Acting Director William Riley, Ph.D.)
Wendy J. Wertheimer, Senior Advisor, Office of AIDS Research (OAR), DPCPSI (representing OAR Director Jack Whitescarver, Ph.D.)
Elizabeth L. Wilder, Ph.D., Director, Office of Strategic Coordination (OSC), DPCPSI

3) *Ex Officio* Member

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH

4) Presenters

Ravi Basavappa, Ph.D., Program Leader, OSC, DPCPSI
James F. Battey, Jr., M.D., Ph.D., Director, National Institute on Deafness and Other Communication Disorders (NIDCD), NIH
Malgorzata Klosek, Ph.D., Director, Division of Construction and Instruments, ORIP, DPCPSI
Kip Ludwig, Ph.D., Program Director, Repair and Plasticity Cluster, Division of Extramural Research, National Institute of Neurological Disorders and Stroke (NINDS), NIH

5) NIH Staff and Guests

In addition to Council members, presenters, and Council Liaisons, others in attendance included NIH staff and interested members of the public.

B. Meeting Procedures

Dr. Grieder reviewed the following:

- Council members are Special Government Employees during Council meetings and therefore are subject to the rules of conduct governing Federal employees.

- Each Council member submitted a financial disclosure form and conflict of interest statement as a Federal requirement for membership on advisory councils. Financial disclosures are used to assess real and perceived conflicts of interest, and Council members must recuse themselves from the meeting during discussion of items for which conflicts have been identified.

- Time has been allotted for discussion between the Council members and presenters, but time for comments from other meeting attendees is limited. The public may submit comments in writing; instructions are available in the *Federal Register* notice for the meeting, which was published on July 22, 2014.

C. Future Meeting Dates

The next Council meeting will be held on January 30, 2015. Subsequent Council meetings in 2015 will be held on June 19and September 1. Council meetings in 2016 will be held on January 29, May 20, and September 9.

II. DPCPSI UPDATE

Dr. Anderson updated the Council about DPCPSI activities. Recruitment is underway for the Associate Director for Behavioral and Social Sciences Research, and Director of OBSSR, who will coordinate and develop NIH policies, goals, and objectives pertaining to behavioral and social sciences research; serve as a liaison between the NIH and the biomedical research community on matters pertaining to behavioral and social sciences research; advise NIH senior leadership on the role of human behavior in the development of health, prevention of disease, and therapeutic intervention; and direct and promote new research areas in the behavioral and social sciences. Dr. Anderson encouraged individuals with the breadth of knowledge and leadership abilities required for this position to apply, requested the Council's help in identifying qualified candidates, and indicated that the review of applications will begin in October 2014.

The NIH has established many programs at the preschool through 12 levels to increase children's understanding of biomedical research and its implications in their lives, as well as to ensure a diverse pipeline of biomedical researchers. The NIH's Scientific Management Review Board, an OD advisory committee (about(about half of its members are NIH Institute and Center (IC) directors has established a working group to review NIH's pre-college biomedical sciences programs, including assessing program attributes and components that are most effective, and determining the points in the education of the pre-college biomedical workforce at which NIH efforts will be likely to have the maximum impact. The working group also will examine and recommend approaches to evaluating the evidence base and effectiveness of these programs. Related to the NIH's efforts to increase pre-college engagement in biomedical sciences, ORIP has issued a funding opportunity announcement for small businesses to

develop serious STEM games as curricula and other tools to help K-12 students learn about health and biology.

Dr. Anderson reminded the Council about the Common Fund planning process and their role in the process. He reported on the status of two concepts discussed during Council meetings earlier in 2014201420142014 and their status in Common Fund planning process. These concepts were recommended by the Council for clearance, and have entered the Phase 2 planning process. One potential program for fiscal year (FY) 2016, the Enabling Exploration of the Eukaryotic Epitranscriptome Program, will explore the role of chemical modification to RNA molecules and the role of these modifications in RNA function and ultimately in health and diseases. The Program's goals are to: (1) generate new tools for monitoring RNA modifications, (2) survey the diversity of RNA modifications, (3) develop computation strategies to predict modifications, (4) explore the biogenesis and function of modifications, and (5) develop small molecule modulators as probes and potential therapies. The second phase of the Science of Behavior Change Program (FY 2015–2019) will develop reproducible models for behavior change, emphasizing adherence to medical regimens.

OSC's upcoming scientific meetings and workshops to determine the approaches that will achieve the highest impacts in proposed programs include: the Physical Activity Workshop to be held October 30–31, 2014; the High Risk-High Reward Symposium to be held December 15–17, 2014; and the Single Cell Analysis Public Workshop to be held April 20–21, 2015.

The NIH is participating in the America Creating Opportunities to Meaningfully Promote Excellence in Technology, Education, and Science (COMPETES) Act Federal challenges. The Act provides agencies with the authority to conduct challenges that stimulate U.S. innovation. The challenges are intended spur innovation, solve problems, advance an agency's core mission, and offer a monetary prize for reaching a goal; agencies benefit by paying only for results and they do not have to predetermine how the goal will be achieved. The NIH's challenge entitled "Follow that Cell," is to identify new and robust methods for detecting and assessing changes in a single cell's behavior and function over time. The challenge is structured as two phases that involve a written description of what the contestant measured and the approach taken (Phase I; $100,000) and a practical application of the method to prove its value (Phase II; $400,000).

DPCPSI staff described recent and upcoming meetings of note, including the 10th Comparative Medicine Resource Directors Meeting hosted by ORIP in August 2014 with the purpose of increasing collaborations and sharing among Division of Comparative Medicine (DCM)-funded resources and identifying resource-related scientific advances on evolving animal-human correlations, emerging technologies, and reproducibility in animal models. Recommendations from the meeting were to improve data sharing and access across resources and with the research community, support phenotyping (phenomics), and consider the future of DCM centers. A colloquium on the recruitment, training, and retention of veterinary scientists was held on July 31, 2014, in conjunction with the DCM's summer veterinary trainees' research symposium. Participants recommended improved data sharing, interdisciplinary training, expanded strategies to fund training and career development programs, and reproducibility training. Upcoming ORIP meetings include a symposium on nonhuman primate models for AIDS and a conference on aquatic animal models of human disease. Dr. David Michael Murray, Director, Office of Disease Prevention, described upcoming Pathways to Prevention workshops covering topics such as the role of opioids in the treatment of chronic pain and myalgic encephalomyelitis/chronic fatigue syndrome. Dr. Janine A. Clayton, Director, Office of Research on Women's Health (ORWH), described an upcoming ORWH workshop on ways to integrate sex as a biological variable in preclinical research. Ms. Wendy J. Wertheimer, Senior Advisor, OAR, highlighted future OAR workshops on basic science, translating research to the community, youth issues, Hispanic communities, women, and synergies between cure research and the basic science of vaccines.

Discussion Highlights

- NIH challenges under the America COMPETES Act are open to individuals, teams, and entities from all U.S. sources, including the public sector, private sector, and nonprofit groups. Intellectual property issues may present challenges for winners associated with institutions because of restrictions on the use of institutional resources. However, the NIH will not retain any intellectual property rights to innovations developed under the challenge.

- The "Follow that Cell" Single Cell Analysis challenge differs from other types of NIH funding in the characteristics of judges, judging criteria, and award timeframe. To date, the NIH has offered small prizes for its challenges, ranging from a few thousand dollars to $80,000. The Single Cell Analysis challenge is the largest that the NIH has offered, and funds for the prizes will be allocated from the Common Fund.

- The Council expressed interest in broadening participation in the Comparative Medicine (CM) Resource Directors Meetings, hosted by ORIP, to include researchers who use resources from the DCM-funded centers. Users and other interested parties can obtain information from the CM Resource Directors' reports covering past meetings, which are available online (http://dpcpsi.nih.gov/orip/cm/reports).

III. KNOCKOUT MOUSE PRODUCTION AND PHENOTYPING: UPDATE AND ENVISIONING A POSSIBLE SECOND PHASE

A. Knockout Mouse Production and Phenotyping: Update and Envisioning a Possible Second Phase

Dr. James F. Battey, Jr., Director, NIDCD, NIH, presented a progress update and potential future plans for the Knockout Mouse Production and Phenotyping ($KOMP^2$) Program. He informed the Council that the predecessor to $KOMP^2$, the Knockout Mouse Production (KOMP) Program, was a high-throughput international effort launched in 2006 by the NIH to produce knockouts for all mouse genes and place the resources in the public domain. KOMP was supported by $56.6 million over 5 years from the ICs with a goal of creating 8,500 embryonic stem (ES) cell lines. The alleles are null or conditional-ready, and they contain a LacZ reporter to evaluate gene expression. A similar program, the European Conditional Mouse Mutagenesis Program (EUCOMM), was launched in October 2005 as a 13 million euro effort with a goal of creating 8,000 mutants. KOMP and EUCOMM, together with other international efforts, formed the International Knockout Mouse Consortium (IKMC), which produced more than 17,000 mutant ES cell lines and made them available from public repositories. KOMP production of ES cell lines surpassed the 8,500 goal. The Program successfully engaged the scientific community, as evidenced by the large number of orders received for vectors (1,250), ES cells (2,512), and mice or germoplasm (980).

The rationale for supporting the subsequent large-scale phenotyping effort of $KOMP^2$ included eliminating redundancy, allowing direct comparisons of a broad set of phenotypes, discovering novel genes, establishing and maintaining quality standards to ensure reliable data, reducing the risk of not finding an interesting phenotype, capturing important but unpublishable negative results, and increasing the potential for breakthrough discoveries. Most knockout mouse strains demonstrate at least one phenotype, with many strains exhibiting between two and five phenotypes. The source of the $110 million funding for $KOMP^2$ is divided almost equally between the Common Fund and participating NIH ICs. Mouse production and phenotyping are being conducted under extramural grants awarded to The Jackson Labs, Baylor College of Medicine, and the University of California, Davis (UCD). The European Bioinformatics Institute manages the Data Coordination Center and Database.

KOMP^2 was envisioned as a two-phase program; the goal of Phase 1 (2011–2015) is to phenotype up to 2,500 mutant lines, while the goal of Phase 2 (2016–2021) is to phenotype 6,000 mutants. All data are freely available through the Data Coordination Center, and the mice are available through a global network of mouse repositories. The nature of the phenotyping is comprehensive, including gene expression, behavior, metabolism, cardiovascular, musculoskeletal, morphology, development, and immune components, among others. The phenotyping pipeline includes different pathways depending on the viability of homozygous mutants. An example of an early success of KOMP^2 is the discovery of 3 new, previously unsuspected genes involved in deafness, as well as 9 genes associated with hearing impairment, and more than 20 genes linked to possible amplitude defects. The significant value demonstrated by the first stage of production and phenotyping strongly supports the Program's continuation.

B. Knockout Mouse Production and Phenotyping: What We Have Done...Where We Are Going

Dr. K.C. Kent Lloyd, UCD, reported on the scientific accomplishments and possible future directions of KOMP^2. KOMP achieved near-complete coverage of the mouse genome, achieving its goal of providing a public resource of ES cells containing a null mutation in 8,500 genes with primarily conditional-ready alleles expressing LacZ. Phenotype data are needed because there is a significant gap in knowledge about human gene functionality, with approximately 75 percent of human genes lacking linkage to animal or human phenotypes, more than 65% of genes lacking functional knowledge in humans and, nearly 90% lacking knowledge related to pleiotropy. KOMP^2 was designed to expand the depth and breadth of functional annotation of the genome. Prior efforts to study gene functionality involved constructing a single mouse knockout, with the phenotyping efforts limited to traits of interest to an individual investigator. Value-added features and benefits of KOMP^2 include broad, genome-wide coverage; validated models; and harmonized and validated phenotyping protocols. These features facilitate transparency, ensure reliability, and emphasize reproducibility. Additional benefits of KOMP^2 include gender-distinguished phenotypes; generation of actionable findings for followup, creation of an infrastructure for testing preclinical models, and real-time, public dissemination of products and data.

The mission of the first 5-year phase of KOMP^2 is to produce and phenotype 2,500 knockout lines, annotating the mouse genome and uncovering associations with human disease, development, and behavior. KOMP^2 includes a data coordination center, mouse production centers, and mouse phenotyping centers. The Program also includes the Mouse Phenotype Informatics Infrastructure Program (MPI2), which is key to coordinating the experimental efforts in disseminating discoveries to the global research community as quickly as possible. The production line begins with KOMP products (e.g., ES cells) that are used to create knockout mouse strains at the production centers. The production centers conduct the initial analysis of homozygous cohorts, analyzing such features as fertility and LacZ expression patterns. The cohorts then are sent to KOMP^2 phenotyping centers for the multi-organ system high-throughput analysis. All of the data and mice are placed in the public domain through the Data Coordination Center. KOMP^2 also participates in the International Mouse Phenotyping Consortium (IMPC), which coordinates international phenotyping efforts through meetings and working groups to minimize overlap and redundant effort and to address topics such as statistical analysis, embryo phenotyping, and anatomical pathology of LacZ expression.

International coordination efforts began with selecting and prioritizing the genes to target through KOMP^2. Highest priority was given to genes that lack functional annotation or disease association. After the gene list was decided for KOMP^2, the knockout constructs were carefully designed using advanced molecular technologies. The two categories of KOMP alleles include the CHORI-Sanger-Davis (CSD) knockout-first conditional allele and the Regeneron VelociGene® definitive null allele. The mouse production pipeline involves producing chimeric mice using the ES cells with the target alleles and

breeding them to yield homozygous cohorts. The production pipeline is at least 1 year ahead of schedule to meet its 2,500-gene target.

An important feature of the allele design includes the LacZ expression cassette, which allows scientists to examine gene expression at a tissue and cellular level in each knockout mouse. Currently, more than 150–170 mutant lines have been analyzed, with 80 percent of them demonstrating specific LacZ expression. Gene expression mapping has been performed in adult animals, as well as in embryos for both viable and embryo-lethal strains. Combined with gene expression mapping, KOMP^2 phenotyping results have revealed new roles for many genes. The IMPC adult core pipelines are established and operational, and baseline control data have been uploaded to the Data Coordination Center. The IMPC has produced phenotyping data on approximately 1,200 mutant lines, and all KOMP^2 centers are processing approximately 15 to 16 strains per week to complete the project on time by August 2016.

Dr. Lloyd presented interesting discoveries from KOMP^2 phenotyping efforts through 11 case studies: (1) a gene with a known disease (Nbeal2); (2) a gene with no known disease (Zfp719); (3) a gene with unknown function (Fam151b); (4) a gene that lacked an existing mouse model (Bbs5); (5) a gene for which the KOMP^2 strain offered a revised model (Atn1); (6) a known gene about which KOMP^2 phenotyping revealed a new phenotype (Cast); (7) a known gene with a new male-specific phenotype (Afmid); (8) a known gene with a new female phenotype (Ccdc33); (9) a known gene with pleiotropic effects (Rabl2); (10) a known gene with new pleiotropic effects revealed (Tead1); and (11) a known gene with a complex phenotype (Galc). In addition to studying a broad range of phenotypes, KOMP^2 has added value by including challenge screening of separate cohorts of mice, as for respiratory challenge. To ensure that the potentially highly informative phenotypes of embryonic lethal and perinatal subviable strains are captured, the KOMP^2 centers established an embryo/subviable phenotyping pipeline for the 30 percent of strains that are homozygous lethal. The strains are evaluated for viability, gross morphology, histopathology, and 3-D imaging at various stages of embryonic development. This triage pipeline captured the cardiac dysmorphology phenotype of the Tmem100 homozygous lethal knockout mouse, as well as the diffuse cerebellar hypoplasia of the Tox3 homozygous subviable strain. From the beginning, KOMP^2 designated one international Data Coordination Center to facilitate the access and use of the data generated by the production and phenotyping centers. The KOMP^2 Data Coordination Center is seamlessly integrated with the IMPC's MPI2 informatics infrastructure. The goals of the MPI2 include providing high-quality data that are freely available in real time; promoting the availability of mice, tools, and protocols generated by KOMP^2; enabling access to a transparent, reproducible statistical analysis; and providing intuitive Web portals and an application programming interface to facilitate data discovery. All of the data can be accessed through IMPC's portal at www.mousephenotype.org.

Mouse and material dissemination has been a priority for KOMP^2. Recently, an online survey was administered to 571 KOMP^2 customers—recipients of mice and germplasm—who provided very positive comments about the program. Within 24 hours, 28 survey responses were received, which indicated that 50 percent of the KOMP^2 materials recipients have a manuscript in progress or published, and 50 percent intend to submit a grant proposal. In addition to the positive comments, the survey captured suggestions for improvements, such as clarification of standard operating procedures. Dr. Lloyd noted that a number of high-profile publications have resulted from the use of KOMP^2 strains, evidence of fulfilling its mission as a launch pad for scientific and technological advances. The advances include adopting new technologies, leveraging newly identified phenotypes to inform new discoveries through other NIH programs, using KOMP^2 mutants as rare disease models, coordinating with other major Common Fund efforts, and assigning function to genes that currently are poorly annotated.

Regarding future directions, Phase 2 of KOMP^2 (2016–2021) aims to complete the mouse genome by creating approximately 6,000 new mouse lines over 5 years. Efficiencies gained in generating new mouse lines will allow less costly production per mutant. KOMP^2 intends to provide a fully validated resource

for the research community, with reliable and reproducible reagents, tools, processes, and data. Metabolic profiling will be performed on a subset of strains, novel technologies such as CRISPR/Cas9 genome editing will be adopted to increase efficiency, and new phenotyping platforms will be developed. Plans also are being made to refine the phenotyping pipeline and improve analysis of behavior, metabolism, and other areas, ensuring continued success of KOMP^2.

Discussion Highlights

- In the first phase of KOMP^2, new technologies are being evaluated to confirm the phenotyping pipeline.

- The Council members expressed interest in ensuring community input on selecting phenotyping assays. When the program was launched, a meeting was held at which the organizers received community feedback as to which phenotypes should be included. Decisions to add new phenotype assays currently are made internally based on whether new assays would add value or replace existing tests. Some phenotyping assays are more robust than others. Less reliable behavioral phenotyping assays, in particular, are being replaced with those that are more robust. There was interest among the Council members about establishing mechanisms by which the community could provide input on phenotyping.

- The IMPC portal, available at www.mousephenotype.org, was built with user feedback and was designed for a diversity of users beyond the mouse genetics community. The website features filtered searches to allow users to find data by gene, phenotype, or disease. Dr. Lloyd welcomed feedback about the site.

- Each gene is examined across all phenotypes. Annotations are added to the database after the knockout mouse has generated phenotype data. There also are linkages to other informatics databases.

- Aging phenotypes are not included because of cost considerations. Researchers can use KOMP^2 models, however, to perform such studies themselves.

- Pilot projects are being done on the effects of stressors on phenotype data. Current work includes a respiratory challenge. Other challenges are ongoing. The Council members suggested that a high-fat diet would be an important additional stressor to consider.

- Data availability from KOMP^2 was discussed. Various data from the program are publicly available, including raw data, positive or negative results, and imaging data. Data are made available to the community as rapidly as possible. Quality control operations must be performed on the data, however, before they are released. To avoid inadvertent bias being introduced by quality control measures, blind filtering is done to the extent possible. All data filtering is based on statistical analyses. These measures ensure that discoveries of new phenotypes are not disregarded. Cross-center comparisons are a prominent feature of quality control.

- Tissue samples are available to the community. Interested researchers should contact the centers about obtaining tissue related to particular diseases or genes of interest.

- The UCD repository has set a precedent that the program is sustainable. The repository was begun with a 4-year grant and now is generating income. From its inception, the UCD was established with a business model that it would become self-sustaining.

- The NIH will conduct a detailed scientific evaluation of KOMP^2 in spring 2015. The presentation will include a summary of the potential contributions and returns on investment of the program.

- Future directions for KOMP^2 include collaborations with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to conduct follow up phenotyping on embryo lethals, and with a Common Fund program to explore the "druggable genome." The NICHD is funding research on subviable, investigator-initiated phenotyping using KOMP^2-produced models via the R01 grant mechanism. The data from these investigations would be included in the KOMP^2 database.

- Existing partners have expressed strong interest in continued participation. Partners include a consortium of centers based in Asia, which has members in South Korea, China, Taiwan, and Japan. In particular, China is projected to increase its funding for biomedical research over the next 5 years to reach levels comparable to that of the NIH.

IV. NIH UPDATE

Dr. Lawrence A. Tabak, Principal Deputy Director, NIH, presented a report on the NIH budget; NIH pilot programs that provide researchers with longer term, stable support; and the need to include males and females in cell and animal research to enhance transparency and reproducibility. In inflation-adjusted dollars, the NIH budget experienced remarkable growth, doubling between FY 1999 and FY 2003, but with the exception of stimulus funding in FY 2009 and FY 2010, the NIH experienced a subsequent decline in support relative to inflation. If the NIH budget had grown steadily at the 3.7 percent rate that prevailed in the 1990s, it would be $10 billion more robust than the current level. Dr. Tabak reminded the Council members that without Congressional intervention, budget sequestration will require automatic Federal spending cuts again in 2016.

To increase support of extramural researchers, the NIH is applying experiences learned from the NIH Director's Pioneer Award (NDPA) Program (Pioneer Awards) to develop mechanisms that enhance flexibility for the investigator, promote risk-taking, provide longer duration support appropriately to allow researchers to focus on conducting the research rather than application preparation, and focus less on project details in the application, with the intent to ameliorate the "perverse incentives" that contribute to the hypercompetitive environment in biomedical research. The NIH also sought to identify existing programs that might be modified or, if less effective, phased out to achieve the goals of ameliorating hypercompetition and enhancing reproducibility.

The Pioneer Awards began in 2004 as one of the first programs of the NIH Roadmap. They were initiated to address concerns that high-risk, visionary research was not being supported and were based on the premise that "person-based" application and review processes would encourage innovation by creative investigators and represent a new mechanism in science management. Before 2004, few analyses of whether different award designs produce different outcomes had been performed. Since then, formal studies have been conducted that demonstrate how to evaluate value for scientific programs and projects, such as "An Outcome Evaluation of the National Institutes of Health (NIH) Director's Pioneer Award (NDPA) Program, FY 2004–2006."[1] These analyses concluded uniformly that higher impact, more innovative science results when applications are shorter and require less preliminary data; review is based on an investigator's prior accomplishments; applicants receive constructive feedback from the review;

[1] https://commonfund.nih.gov/sites/default/files/P-4899_Final_Redacted.pdf.

grants provide more support with longer durations, allowing the investigator to focus on the work rather than securing funding; and principal investigators (PIs) have flexibility to change direction. Other agencies have adopted this type of award.

In a recent blog entry, Dr. Collins described the nature and benefits of longer term, stable support. Historically, most NIH-funded grants have been project-based and funding typically lasted 3 to 5 years. The NIH recognized that the average NIH award under the R01 grant mechanism was insufficient to support an entire research program in many fields of science. Internal discussion at the NIH resulted in several NIH ICs developing new funding opportunities to offer more sustained support, with each IC's approach being tailored to its mission. Pilot programs include the National Cancer Institute's (NCI) Outstanding Investigator Award and the National Institute of General Medical Sciences' (NIGMS) proposed Maximizing Investigators' Research Award Program.

Dr. Tabak next discussed an NIH strategy to include males and females in cell and animal research. Biology research traditionally has been conducted in the laboratory using male cells and animals, and in the clinic, the "70 kg" male has been used as being representative. However, members of minorities are not "non-Whites and women are not "non-males." The potential biases of this male-centered approach need to be assessed to ensure results that are rigorous and reproducible. The NIH's plans to enhance reproducibility, as outlined in a *Nature* commentary by Drs. Collins and Tabak, include assessing the effect of sex differences. Dr. Tabak illustrated the problem by citing a study in which a kinase inhibitor was tested in a cohort consisting solely of males. An examination of the literature revealed male domination of studies in 8 out of 10 biological disciplines.

Reasons to research sex influences are multiple, for example, many significant factors in diseases are related—or unrelated—to reproduction. In addition, it is unknown what researchers are missing by not including sex factors. An example of a success story is preclinical results from the Interventions Testing Program at the National Institute on Aging, which found that 17α-estradiol and aspirin extend the lifespan only in males, whereas rapamycin extended the lifespan in both genders—results that would have been obscured without the appropriate experimental setup and data analysis.

The NIH's approach to study both males and females in cell and animal studies is explained in a commentary in *Nature* by Drs. Collins and Clayton. The issue has attracted significant public discussion in the scientific and lay press, and been addressed in the Research for All Act, which amends the Public Health Service Act to enhance the consideration of sex differences in basic and clinical research, requires the NIH to issue guidelines and track statistics, and codifies the NIH Special Centers of Research on Sex Differences. The ORWH provides the latest news about the NIH's efforts in this area on its website and is partnering with NIH ICs to improve the way in which sex differences are addressed in research through Specialized Centers of Research and administrative supplements. Common Fund supplements for sex difference analysis, totaling approximately $4 million in FY 2014, will support a range of programs. Dr. Tabak encouraged Council members to serve as spokespersons to their institutions and professional societies on this topic.

V. DISCUSSION

The consequences of including males and females in cell and animal research were discussed. Although including both sexes would increase the number of animals needed in each study, doubling the number of animals would not be necessary in every study. Results will need to be reported in a sex-specific, sex-disaggregated way, but not every study would be powered to test sex differences.

There are multiple reasons why more female-derived data are needed. Mixing data from both sexes can lead to inaccurate interpretations and missed insights. Without disaggregated data, physicians have insufficient data to determine proper medication dosages, which affect men and women.

Common Fund supplements for sex difference analysis will be provided for relevant studies conducted solely on male animals to address the imbalance in the data. The NIH review process also will be used to ensure that new studies address sex differences where appropriate. The Center for Scientific Review is tasked with ensuring that Scientific Review Officers understand the issue, and a trans-NIH Working Group has been formed to ensure that this issue is addressed. The NIH plans to use a phased approach, recognizing that new tactics should be science-based, feasible, and implementable.

Racial differences are another factor to consider in study design. These apply to the rates and trajectories of diseases, as well as responses to intervention. A data repository could be designed to focus on gender and other issues and be used to inform treatments based on different traits. The NIH recognizes the importance of considering diversity in research. Developing a data commons with data that could be interrogated remotely is one of the NIH's long-term goals.

The Council members emphasized the benefits of sustained funding for longer term research. Some research questions, such as factors affecting sexually transmitted disease transmission and measures to reduce incarceration rates, can be explored only through long-term studies. Sociobehavioral research in particular requires timespans greater than 5 years. The NIH has sought approval to extend clinical trials up to 7 years. Extending the timescale of support must be balanced, however, against the need for adequate resources to invest in promising new areas of research. One solution might be to adjust funding levels for long-term projects over time. Another need is to provide opportunities to support young investigators and investigators from groups who are underrepresented in the biomedical research community. The NIH's models have shown a decline in success rates when more funds are committed to long-term projects. The Council emphasized the importance of the project- and goal-oriented approach of the Common Fund over budget-driven funding. Sustained funding only will apply, however, to part of the NIH's portfolio. Alternative funding mechanisms such as the NDPA Program have been proven successful.

The concept of a "last award" was proposed by the Council. This award would plan for funding the training of protégés by mentors who are at the end of their careers. Once challenge in executing the concept is that researchers are staying professionally active for longer periods of time than in the past.

The downsizing of the scientific enterprise in the United States is a challenge facing the biomedical research community. Given the current fiscal constraints, the NIH is studying employment options other than the traditional academic path for trainees. The NIH has limited control, however, over hiring practices in the extramural community. Other countries provide examples of research funding models that the United States could consider.

VI. ENHANCING REPRODUCIBILITY—UPDATE

Dr. Anderson provided an update regarding NIH-wide activities to enhance reproducibility and transparency in its research activities. The Common Fund supports research to collect new data and analyze existing data to determine when it is important to consider gender differences. KOMP and the Genotype-Tissue Expression (GTEx) Program, for example, have generated large data sets that can be used to determine when gender is important for understanding research results. Challenges in research reproducibility received significant attention several years ago because industry was unable to validate drug targets produced by NIH-funded researchers, a problem attributed to poor study design. In response,

the NIH initiated pilot studies, and the Council was asked to consider whether these pilots were addressing the problem or if DPCPSI should adopt other approaches.

In a recent commentary in *Nature*, Drs. Collins and Tabak discussed these initiatives, which had generated a positive response from the community. Numerous activities have been undertaken at a trans-NIH level, including a workshop to identify journal practices that affect research quality and reproducibility. The workshop resulted in a set of principles and guidelines that are in review by journal boards. Among trans-NIH stakeholder engagement activities, the NIH plans a meeting with representatives from the pharmaceutical industry and with reagent suppliers. NIH presentations on engaging stakeholders are scheduled at the Virginia Commonwealth University and Society for Neuroscience. An example of efforts to increase transparency by the extramural research community is the Center for Open Science (COS). The Reproducibility Project: Cancer Biology, a collaboration between COS and the Science Exchange to independently reproduce 50 high-impact cancer biology studies, demonstrates the research community's active interest in reproducible and validated results.

Dr. Anderson highlighted activities relevant and complementary to the NIH's reproducibility efforts. Basic training modules for intramural use at the NIH and talks in TED-MED style on data interpretation considerations are in preparation, and the Foundation for Advancing Education in Science has produced graduate-level courses for NIH staff on improving reproducibility. Longer grants might help the issue, and the NCI recently launched a 7-year Outstanding Investigator Award Program. In addition, the Center for Scientific Review is developing checklists to streamline the grant review process. Examples of pilot projects relevant to reproducibility include the NIH projects considering sex as an independent variable and NIGMS' reproducibility in cell culture studies that found major repositories reported contamination in a significant fraction of submitted cell lines. Other ICs are supporting complementary efforts, such as NIDDK's National Mouse Metabolic Phenotyping Centers, which provide standardized, high-quality phenotyping services.

Discussion Highlights Regarding Enhancing Reproducibility

- Increased awareness and training on reproducibility are needed in the veterinary community. Veterinarians are well informed about the limitations and needs of animal models. Veterinarians who are PIs or partner with PIs could influence the study design to enhance reproducibility.

- The National Academy of Sciences' Institute for Laboratory Animal Research Roundtable on Science and Welfare in Laboratory Animal Use is addressing the issue of reproducibility via a workshop and follow-up efforts aimed at developing targeted action items.

- Increasing the duration of research grants would alleviate pressure on PIs but would not address the needs of postdoctoral researchers.

- NIH-funded core facilities provide a potential focus for increasing awareness of reproducibility issues and proper use of data.

- Lack of reproducibility issues could potentially overlap with fraud. The NIH does not have regulatory authority, however, over instances of fraud.

- The use of multiple methods can be an effective approach to enhancing reproducibility, but variability of results derived from different methods need to be understood, which requires the use of statistical analyses. Stronger knowledge about statistics in the scientific community and among individual investigators is important.

Other Discussion Highlights

- A candidate vaccine to protect against the Ebola virus has been developed by the NIH in collaboration with GlaxoSmithKline. Prior to the outbreak in West Africa, the vaccine was not scheduled for human safety trials. Recently, however, the U.S. Food and Drug Administration (FDA) has given permission for the experimental vaccine to be tested on human volunteers. Preliminary results are expected at the end of 2014 or early 2015.

- At the June 2015 Council of Councils meeting, Dr. Jon R. Lorsch, Ph.D., Director, NIGMS, NIH, will speak about his perspective as the new Director of an NIH Institute.

VII. UPDATE ON STIMULATING PERIPHERAL ACTIVITY TO RELIEVE CONDITIONS (SPARC)

Dr. Elizabeth L. Wilder, Director, OSC, DPCPSI, provided an overview of the Stimulating Peripheral Activity to Relieve Conditions (SPARC) concept that the Council approved at its June 2014 meeting. The SPARC Program is funded under the Other Transaction Authority (OTA), a funding mechanism that allows cutting-edge research from commercial sources. The NIH collaborated with GlaxoSmithKline to organize a symposium that allowed the NIH to move rapidly forward with the SPARC concept.

Dr. Kip Ludwig, Program Director, Repair and Plasticity Cluster, Division of Extramural Research, NINDS, NIH, introduced the SPARC Program by noting the current excitement among researchers and the popular press about the potential therapeutic benefits of "electroceuticals," which also are called "bioelectronic medicine." A 2013 *Nature* paper authored by neuromodulation experts detailed a vision for implantable devices to interact with the nervous system to manipulate organ function in disease conditions. Nerve stimulation is not a new idea; the original work was published in 1970 describing the effect of carotid sinus nerve stimulation on angina. Industry also has explored the therapeutic potential of nerve stimulation for conditions as diverse as urinary incontinence, obesity, diabetes, and hypertension.

Recent FDA approvals for randomized controlled trial (RCT) Pivotal Trials have been granted for the treatment of sleep apnea, sight restoration, and seizure treatment. Several treatments approved in Europe, however, have not met primary efficacy endpoints in U.S. RCT Pivotal Trials. Examples include Medtronic's SYMPLICITY (designed to treat hypertension), which showed a large placebo effect; DEBuT by CVRx®(designed to treat hypertension), which showed no significant difference in the primary endpoint but positive results for the secondary efficacy endpoint in patients unresponsive to other therapies; Enteromedics' EMPOWER (designed to treat obesity), which showed significant results but not enough to offset the risks of surgery; and BROADEN/RECLAIM Trials (designed to treat depression), which also failed. CVRx® Neo is a minimally invasive device that has shown a remarkable acute response in a small subset of patients, as Dr. Ludwig demonstrated in a video of the effect of short-term nerve stimulation on reducing blood pressure in a patient. These positive results typify the problems that need to be addressed for electroceuticals; knowledge is limited about the nerves being stimulated and patient-associated factors that influence efficacy.

One of the problems in nerve stimulation therapies is resolution. Although battery size has improved substantially, electrode resolution has not. Certain nerve topographies enable the development of high-resolution devices: the retina, for example, has a functional map that is consistent from patient to patient, whereas the unknown distribution of fibers in the vagus nerve creates a barrier to the creation of a high-resolution device because of unknown benefits, risks, and costs.

Dr. Ludwig described efforts to refine the SPARC Program. The objective of the SPARC Program is to integrate functional anatomical neural circuit maps in organ systems and develop and pilot new electrode

designs. The Bioelectronic Medicine Summit held in December 2013 was well attended, indicating the breadth of interest in the concept. The Summit participants helped the NIH to identify and prioritize key research challenges. Summit recommendations included creating a visceral nerve atlas to enhance fundamental understanding and establish relevance of models; advancing interface technology to allow imaging on a microscale level, sensing of organ function, and development of visceral control modules; and establishing therapeutic feasibility, starting with early feasibility studies of effects in models with low resolution. NIH and non-NIH portfolio analyses revealed that NIH invests approximately $100 million annually in neuromodulation therapy, primarily for pacemakers and defibrillators; approximately $120 million per year in neural innervation of visceral organ systems; and $10 million annually in translating next-generation technology to visceral nerves. Other ongoing efforts include Defense Advanced Research Projects Agency (DARPA) funding by the U.S. Department of Defense to develop sensory prosthetics and GlaxoSmithKline "quick fail" efforts for multiple diseases using a variety of model systems. The expertise in biology (e.g., organ function, anatomical innervation in humans and animal models, surgeons with expertise in nerve access for each organ, computational modeling of neural activity and organ function, and post-mortem tracing in humans) and technology (e.g., electrode design, implantable optogenetic platforms, voltage probes, noninvasive imaging, and clinical devices for functional mapping) required for the program is broad. This creates an ideal opportunity to use the OTA mechanism to build a flexible structure with active management for the program.

The SPARC program is comprised of four initiatives. The first initiative, "Biology," will involve three stages: (Stage 1) "Vision-Setting" Grants to assess current knowledge, identify opportunities for anatomic and functional mapping, and assess inter-individual variability; (Stage 2) Mapping Using Existing Technology, including initial low-resolution functional mapping, development of organ-specific technology to measure organ function, and integration of reverse translational projects; and (Stage 3) Functional Mapping With Next-Generation Tools, Design and Piloting of New Therapies, including higher resolution functional mapping. The three stages of the second initiative, "Next-Generation Tools/Technology," are the following: (Stage 1) Vision-Setting Grants to plan for scalable and sustainable manufacture and integrating technology with the needs for the Biology initiative; (Stage 2) Short-Term Development, including robust, wireless low-resolution recordings and stimulation; and (Stage 3) Long-Term Development of a wireless, high-resolution system, techniques for cell-type specific manipulation in animal models, and microendoscopic tools for minimally invasive surgeries. The third initiative, "Clinical Demonstrations for Small Market Indications," will involve applying developed technologies to other applications. The fourth and last initiative, "Data Coordination,"—one of the most important outputs—will depend on the organ(s) chosen and coordination with the community. The planned budget for the SPARC Program involves pilot funding for FY 2015 that would be increased in the subsequent years for a total investment of $248 million over 6.5 years. In FY 2015, the SPARC Program plans to issue a Request for Information from interested academic and industry partners, conduct outreach, recruit a program manager, issue an announcement(s) for applications, and make awards for Stage 1 research projects. The SPARC Program has been a true trans-NIH effort.

Discussion Highlights

- Future plans for the SPARC Program include enlisting physicists and mathematicians to envision the new technologies such as noninvasive imaging.

- Industry, FDA, and basic scientists have been critically involved in the development of the SPARC Program.

- Although there are FDA-approved devices for SPARC therapies, the biological mechanisms behind their efficacy are not well understood. The NIH's role in SPARC technologies is to invest

primarily in preclinical and basic academic research—long-term investments that are not of interest to industry—with the goal of developing better therapies.

- One explanation for the large placebo effects is the difficulty in blinding patients because of the side effects from the nerve stimulations.
- The dramatic acute results point to a promising future for these therapies.
- The first initiative of the program will identify the best therapeutic opportunities. One criterion will be to target organs for which technologies are minimally invasive.

VIII. REVIEW OF GRANT APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[2] Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Council would represent a real or perceived conflict of interest. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect. The *en bloc* vote for concurrence with the initial review recommendations was affirmed by all Council members present. During the closed session, the Council concurred with the review of 181 ORIP applications with requested first-year direct costs of $62,487,019.

IX. REVIEW AND VOTE ON COUNCIL OF COUNCILS OPERATING PROCEDURES FOR 2015

Dr. Grieder introduced three proposed revisions to the Council of Councils Operating Procedures:

- Clarifying ORIP applications that were eligible for Early Concurrence review by adding the phrase "i.e., those with scores of 45 or better" (Section II.G.1.a).
- Defining situations for which Council concurrence is enlisted for administrative supplements by adding the conditions of administrative supplements being in excess of $500,000 or greater than 50 percent of the direct costs of the parent award as the defining situations for which Council concurrence will be enlisted. (Section IV.C. D).
- Removing unclear and vague text (e.g., "administrative decisions") by deleting part H. Also address concerns by stipulating that the Council be informed of "all" administrative decisions made by DPCPSI that would subject the Council to an undue burden (Section IV.H).

Discussion Highlights

- DPCPSI developed the proposed definition of situations under which Council concurrence should be enlisted for administrative supplements by surveying the policies of other institutes.

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[2] For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure applied only to applications that were discussed individually, not to "*en bloc*" actions.

- Administrative decisions related to funding are distinct from administrative supplements, which do not undergo peer review. Administrative funding decisions may be made under specific circumstances, such as when an application is withdrawn or when two applications receive essentially the same score.

- The proposal to delete the reference to listing all administrative decisions was made because the decisions to which it applied was unclear. Taken literally, it would obligate the Council to review all of DPCPSI's grant-related administrative actions.

Vote

A motion to approve the proposed revisions to the Council of Councils Operating Procedures was forwarded and seconded. The motion passed unanimously, and the revisions were approved.

X. UPDATE ON NIH-SPONSORED RESEARCH CORE FACILITY ACTIVITIES

Dr. Anderson provided an update on NIH-sponsored research core facility activities. Two workshops sponsored by the National Center for Research Resources (NCRR) and Office of Extramural Research in 2009 and 2010 solicited input from the extramural research community regarding efficient management and use of NIH-sponsored core facilities. Because NIH ICs have established similar core facilities at specific institutions, duplication and underutilization of distinct cores can occur. In addition, confusion exists regarding the implementation of Office of Management and Budget circulars about expenses and legal issues relevant to the cores.

The lack of a coordinated approach to the multiple core facilities presents a serious challenge. In FY 2013, the 30 institutions that received the highest levels of funding through P30, P50, P60, and U54 mechanisms represented awards in the approximate amount of $2 billion in total costs, with funding in each of the parent awards allocated among administration, training, research, and support of the core facility.

A deeper analysis was performed on FY 2012 funding data of P30 grants awarded to three universities, which received an aggregate of 38 awards for 155 shared-resource cores. One of the institutions had two NIH-funded core facilities devoted to sequencing, two to mass spectrometry, and three histology core facilities that provided unique and standard services; these were identified through the NIH funding database, IMPAC II; however, broader searches using Google, RePORTER, and searches of the institution's and core facilities' websites revealed additional histology core facilities that were funded through a no-cost extension, had an ambiguous database title, were Clinical and Translational Science Award (CTSA)-supported, were associated with a Comprehensive Cancer Center, or were provided by the institution's Pathology Department. Funding data and the analysis of possible overlap among NIH-funded core facilities at institutions indicate that a significant level of NIH support is allocated to core facilities and that redundancy exists but is difficult to document. The NIH does not collect data systematically that could inform opportunities for sharing facilities, and databases are difficult to search for this information. In addition, not all core facilities should be shared, and although some informed institutions have been motivated to share core facilities, management practices and financial incentives vary.

Dr. Anderson stated that administrative supplements issued under the American Recovery and Reinvestment Act (ARRA) in 2009 by the NIH solicited applications to consolidate cores for greater efficiency. Criteria included that the consolidated core facilities be made widely available and operate within the scope of the parent grant. A total of 80 applications were received, and 26 awards ranged from $300,000 to $1.3 million. Institutions receiving ARRA core consolidation supplements provided

information about the consolidation's effect on space, services, training, and other data in their final progress reports. Most institutions consolidated two core facilities, although some consolidated as many as five core facilities; facilities also were consolidated successfully across multiple institutions. Institutions reported more efficient facilities following consolidation, as seen in increases in users and services. An analysis of processes centralized as a result of consolidation found management efficiencies gained in billing (72%), purchasing (75%), services scheduling (92%), and services tracking (92%). Fourteen institutions reported gains in income after consolidation, and two increased by more than 1,000 percent. In addition, a majority (73%) of the core facilities reported that they increased in physical size and staffing, although five awardees reported a decrease in staffing as a result of the consolidation.

Dr. Anderson reflected on the core facilities consolidation effort, which requires an investment of funds. Successful consolidation allows best practices to be disseminated via standard operating procedures, results in cross-trained and better prepared staff, improves communication, allows core facilities to provide services more quickly, and enhances data analysis. He noted that a full report on the results from the consolidation awards is forthcoming, and encouraged the Council to consider consolidation opportunities at their institutions as well as obstacles and incentives to affect a cultural shift among investigators and institutions.

Discussion Highlights

- The initiative to consolidate NIH-sponsored core activities generally will originate at the institutional level as most PIs have little incentive to initiate consolidation activities. Heads of core facilities might take the lead as well.
- Removing restrictions on the use of equipment would facilitate consolidation.
- A database of NIH-sponsored core facilities could provide information to applicants about other core facilities at their institutions. The database could be organized by resources provided, such as specific instrumentation. Applicants could be required to justify the reasons why they cannot use existing core facilities.
- Applications to establish NIH-sponsored core facilities are scored based on potential users. It would be valuable to verify that listed users made use of a given facility.
- Although some NIH-sponsored core facility functions, such as purchasing and management, might be easy to consolidate within institutions, reasons exist for maintaining separate core facilities within a location. These include disease containment, dedicated use for animals, and multiple locations (e.g., The Johns Hopkins School of Medicine is housed in multiple buildings). Some types of core facilities (e.g., bioinformatics) might be easier to merge than others.
- UCD provides an example of an institution that successfully merged overlapping NIH-sponsored core facilities and achieved cost savings.

XI. REFLECTIONS FROM MEMBERS ROTATING OFF THE COUNCIL OF COUNCILS

Ms. Burton, Dr. Mitchell, Dr. Lloyd, and Dr. Murphy reflected on their experiences serving on the Council of Councils, offered suggestions to improve the ability of Council members to give their input, and provided advice to new Council members.

Ms. Burton expressed appreciation for her experience as a Council member. Previously, she had served on the National Diabetes and Digestive and Kidney Diseases Advisory Council and had prior experience at the Department of Health and Human Services. She emphasized the importance of communication by the research and advocacy communities and encouraged their greater involvement in the NIH's advisory process, particularly strategic planning. Ms. Burton reflected on the need for prevention, education, and awareness about disease, and participation on the Council helped her consider how to build relationships and better align National Kidney Fund initiatives with NIH and Centers for Disease Control and Prevention activities. She encouraged staff to provide ongoing guidance regarding the Electronic Council Book (ECB) and review of summary statements.

Dr. Mitchell joined the Council in the midst of the transition from NCRR to ORIP, and she reflected on shifts in the role of Council members during that time. She suggested that Council agendas allow more time for discussions about Common Fund concepts and projects, and encouraged the Council's involvement in more discussions and consider having Working Groups help to connect the Council with more programs.

Dr. Lloyd appreciated his time on the Council. He recommended more time for discussions on topical issues and suggested sending materials to members in advance of the meeting. He stated that the Common Fund Working Group model had worked well and observed that a brief summary report and action items following each Council meeting would be useful. He suggested that Council members might serve as effective advocates for biomedical research and should be prepared to handle issues regarding sequestration. Dr. Lloyd commented that the Council could assist with developing the meeting agenda, and he thought time might be saved by scheduling the closed session review as the first agenda item. He indicated that statistics on projects that were funded under programs that were cleared by the Council would be of interest to members.

Dr. Murphy characterized the Council of Councils as being fundamentally different from other advisory councils and suggested that new members take advantage of the expertise of other members when needed. He also encouraged new members to rely on the DPCPSI staff to solicit the type of feedback the NIH needed from the Council.

The outgoing Council members made the following suggestions on how to improve the experience and effectiveness of Council members:

- Provide more materials in advance electronically.
- Allow more time to discuss Common Fund concepts during the approval process.
- Increase the involvement of Council members in concept development (e.g., the SPARC Program developed from a single-page description to a full presentation with no input from the Council).
- Produce a brief summary report from Council meetings that would be less detailed than the official minutes and that would contain action items.
- Orient new Council members by providing them with a written primer.
- Conduct the closed session first.
- Provide opportunities to Council members to suggest agenda items.
- Encourage interested Council members to be available to the NIH for service as emeritus Council of Council members.

XII. EARLY INDEPENDENCE AWARD PROCESS EVALUATION AND DISCUSSION

Dr. Ravi Basavappa, Program Leader, OSC, DPCPSI, reported on initial results from the evaluation of the NIH Director's Early Independence Award (EIA) Initiative. Dr. Collins conceived of the EIA Initiative as a catalytic program that would allow exceptional young investigators to start their independent research careers more quickly. The design of the EIA Initiative was informed by an NIH-sponsored workshop. Three funding models were considered: (1) a matchmaking model whereby institutions and fellows would apply in parallel; (2) a fellow-driven model where candidate fellows would be reviewed by the NIH, successful fellows would find a suitable institution, and the institution would be reviewed by the NIH for suitability; and (3) an institution-driven model where potential host institutions would be reviewed by the NIH and then identify candidates. The Independent Fellows Program concept and workshop recommendations were presented to the Council of Councils in July 2010; the Council expressed concerns about "rich" institutions being favored and proposed a hybrid approach in which an institution would apply and include one individual as the institution's first choice, highlighting the candidate's suitability in the application. The resulting EIA Initiative established criteria for candidate and host institution eligibility: the candidate must be within 12 months of finishing his or her terminal research degree or medical residency, the host institution was allowed up to two applications, the candidate and host institution must prepare the application together, and the review process would focus on the qualities of the candidate as well as the support and commitment of the host institution.

Under the Initiative, awards have been made for 3 years, providing sufficient data to evaluate its efficacy. Unexpectedly, a significant fraction of applicants had established research programs as independent fellows or held assistant professorships. In evaluating the Initiative, the applicants were divided into two groups: not independent (graduate students, postdoctoral fellows, and residents); and independent (independent fellows, assistant professors, and others such as lecturers and intramural researchers). Segregated this way, slightly more than one-half of all applicants were characterized as not independent.

Analyzing the independence status of awardees indicated that the review process favored independent applicants. Several of the awardees who were postdoctoral researchers or graduate students at the time of application already had made arrangements to become assistant professors, and the NIH determined that the award accelerated entry into independence for less than one-third of awardees, with a trend toward declining success over time. Although there were 29 distinct host institutions for 39 awards, the host institutions were located preferentially in the San Francisco, California, and Boston, Massachusetts, areas.

At a conference convened to analyze EIA results and determine future actions, participants did not reach consensus about the success of the EIA Initiative. Points made in the discussion included that the Initiative design has no apparent fundamental flaw, eligibility of candidates is subject to interpretation, funding an EIA institutional fellow can permit an additional institutional fellow to be funded, and the institution-driven model should be considered as an additional funding model. The conference participants recommended that data be collected for an additional year, followed by an update report to the Council. Dr. Basavappa asked the Council to provide input on the Initiative's eligibility criteria and future NIH considerations.

Discussion Highlights

- The EIA provides a unique funding mechanism that allows highly talented awardees to bypass postdoctoral research and proceed directly to an entry-level faculty position. These awards are designed to encourage institutions to invest in the awardees. Receipt of the award generally does not affect hiring decisions, as most awardees already had accepted offers for academic positions at the time of the award, having been recognized by their hiring institutions as "superstars." In

addition, the chosen specialty of applicants will have a strong effect on success in securing an academic position.

- In contrast to the EIA, the K99/R00 funding mechanism facilitates the transition from postdoctoral research to a faculty position.

- The appropriate definition of "independent" was discussed extensively. The degree of independence of first-year faculty members depends on the field of research. First-year clinical researchers usually are supported by their departments, whereas researchers in basic science typically are independent in their first year. The Council members recognized the impressive qualifications of awardees, but noted that it will be difficult to determine whether the Initiative fosters independence if awards are made to those who already are independent. Criteria for eligibility should be clarified for the review panel.

- The Council suggested that it was too early in the Initiative to determine whether the award process was fostering sustainable independence. A metric of success might be the number of R01 grant applications awarded to EIA recipients as opposed to K99 awardees. It was questioned whether the size of the Initiative was sufficient to uncover statistically significant differences in success rates.

- The EIA could be used by the NIH to address the limited diversity of the biomedical workforce. None of the awardees, however, were affiliated with historically black colleges and universities or other minority-serving institutions.

- By alleviating the financial pressures associated with large amounts of student debt, the EIA also might address the tendency of newly graduated physicians to select careers in clinical practice over academic research.

- DPCPSI will continue to update the Council on the progress of the EIA Initiative.

XIII. HIGH-END INSTRUMENT FUNDING OPPORTUNITY—UPDATE ON THE PLANNING PROCESS

Dr. Malgorzata Klosek, Director, Division of Construction and Instruments, ORIP, DPCPSI, described progress in the planning process for the High-End Instrumentation (HEI) Program. ORIP manages two NIH's S10 Programs: HEI Program and Shared Instrumentation Grants Programs ; their goal is to fund grants to purchase expensive instruments that will be used on a shared basis, with the grantee institution being responsible for funding the warrantee, maintenance, and technical staff. The HEI Program was launched in 2002, focusing on a new generation of instruments that were not widely available and on which only a limited number of investigators had expertise. Between FY 2002 and FY 2013, the Program issued approximately 200 awards, with a total budget of approximately $300 million, and in FY 2014, the Program had a budget of $24.5 million, supporting 16 awards. The HEI Program supports a variety of technologies, with approximately one-third of requests and awards being imaging technologies, such as computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). The most recent program announcement had a due date of September 2013 and approximately 100 applications were received; these were reviewed in the winter of 2014 and approved by the Council in June 2014. From that group of applications, 16 grants were awarded in FY 2014 for a total budget of $24.5 million; ORIP expects to fund additional 15 grants in FY 2015

Receipt rates for the HEI Program could be changed from biannual to annual. The plan is to award the same number of grants each year, but it is unclear whether this change would affect the number of

applications and the resubmission rate. The program is seeking comments from the Council on this proposed change.

Discussion Highlights

- Currently, the HEI Program receives approximately 100 applications per funding solicitation. Applicants who are unsuccessful currently must wait 2 years before submitting a new application. The rate of resubmittals is 1 to 3 percent.
- Administrative costs for the program will increase if solicitations are issued annually rather than biannually.
- An annual schedule for solicitations might ensure that the program funds the most up-to-date technologies. Technology might change significantly in 2 years.

XIV. CLOSING REMARKS

Dr. Anderson thanked the Council members and speakers for their contributions at this meeting. He reminded the members that the next Council meeting will be held on January 30, 2015.

XV. ADJOURNMENT

Dr. Anderson adjourned the meeting at 4:05 p.m. on September 5, 2014.

XVI. CERTIFICATION

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

James M. Anderson, M.D., Ph.D.
Chair, NIH Council of Councils
Director, DPCPSI, OD, NIH

10-30-2014
Date

Franziska B. Grieder, D.V.M., Ph.D.
Executive Secretary, NIH Council of Councils
Director, ORIP, DPCPSI, OD, NIH

10/30/2014
Date