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 9, 2016

Meeting Minutes

I. CALL TO ORDER AND INTRODUCTIONS

Robin I. Kawazoe, Deputy Director, DPCPSI, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. The meeting began at 8:30 a.m. on Friday, September 9, 2016, in Building 31, Conference Room 10, on the NIH Campus in Bethesda, Maryland.

Ms. Kawazoe welcomed members and noted that Dr. Anderson, Dr. Boerwinkle, and Mr. Contreras were unable to attend the day's meeting. Dr. Judy E. Garber participated via teleconference for part of the meeting. The meeting attendees are identified below. Ms. Kawazoe also announced that the Director's Report had been provided to members, and she encouraged that they share the report with colleagues.

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

A. Attendance

1. Council Members

Council Members Present

Chair: Robin I. Kawazoe, Deputy Director, DPCPSI, representing **James M. Anderson, M.D., Ph.D.,** Director, DPCPSI
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
Sharon Anderson, M.D., Oregon Health & Science University, Portland, OR
Marlene Belfort, Ph.D., University of Albany, Albany, NY
Melissa Brown, M.D., M.N., M.B.A., Thomas Jefferson University, Flourtown, PA
Molly Carnes, M.D., M.S., University of Wisconsin–Madison, Madison, WI
Ana M. Cuervo, M.D., Ph.D., Albert Einstein College of Medicine, Bronx, NY
Jonathan Epstein, M.D., Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
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
Hakon Heimer, M.S., Schizophrenia Research Forum, Providence, RI
King K. Holmes, M.D., Ph.D., University of Washington, Seattle, WA
Terry L. Jernigan, Ph.D., University of California, San Diego, La Jolla, CA
Norma Sue Kenyon, Ph.D., University of Miami School of Medicine, Miami, FL
Vivian S. Lee, M.D., Ph.D., M.B.A., University of Utah, Salt Lake City, UT

Kimberly K. Leslie, M.D., University of Iowa Hospitals and Clinics, Iowa City, IA
Guillermina Lozano, Ph.D., The University of Texas MD Anderson Cancer Center, Houston, TX
Terry Magnuson, Ph.D., University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC
Norbert J. Pelc, Sc.D., Stanford University, Stanford, CA
John Postlethwait, Ph.D., University of Oregon, Eugene, OR
Keith A. Reimann, D.V.M., University of Massachusetts Medical School, Boston, MA
J. Leslie Winston, Ph.D., D.D.S., The Procter & Gamble Company, Mason, OH
Nsedu Obot Witherspoon, M.P.H., Children's Environmental Health Network, Washington, D.C.
Gail Yokote, M.S., University of California, Davis, Davis, CA

Council Members Absent
Chair: James M. Anderson, M.D., Ph.D., Director, DPCPSI
Eric Boerwinkle, Ph.D., The University of Texas Health Science Center at Houston, Houston, TX
Jorge Contreras, J.D., University of Utah, Salt Lake City, UT

2. Liaisons

Abby Ershow, Ph.D., representing **Paul M. Coates, Ph.D.,** Director, Office of Dietary Supplements (ODS), DPCPSI
Maureen M. Goodenow, Ph.D., Director, Office of AIDS Research, DPCPSI
David M. Murray, Ph.D., Director, Office of Disease Prevention (ODP), DPCPSI
Wendy Smith, M.A., Ph.D., BSB, representing **William Riley, Ph.D.,** Director, Office of Behavioral and Social Sciences Research (OBSSR), NIH
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

Carlos Blanco, M.D., Ph.D., Director, Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse (NIDA), NIH
Robert Carter, M.D., Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH
Eric Dishman, Director, Precision Medicine Initiative® (PMI) Cohort Program, OD, NIH
Malgorzata Klosek, Ph.D., Director, Division of Construction and Instruments (DCI), ORIP, DPCPSI
Kimberly K. Leslie, M.D., Council of Councils Member
Jon Lorsch, Ph.D., Director, National Institute of General Medical Sciences (NIGMS), NIH
Scott Lowe, Ph.D., Chair, Geoffrey Beene Cancer Research Center, Memorial Sloan Kettering Cancer Center (MSKCC)
Oleg Mirochnitchenko, Ph.D., Program Director, Division of Comparative Medicine (DCM), ORIP, DPCPSI
Stephanie Murphy, V.M.D., Ph.D., Director, DCM, ORIP, DPCPSI
Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, 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. Announcements and Updates

Dr. Grieder reviewed the following:

- Council members are Special Government Employees during the days of 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 in compliance with Federal requirements for membership on advisory councils. The financial disclosures are used to assess real and perceived conflicts of interest, and Council members must recuse themselves from the meeting during discussions of any 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 29, 2016.
- Minutes from the May 20, 2016, meeting have been published on the DPCPSI website. The minutes from this meeting also will be published there.

C. Future Meeting Dates

The next Council meeting will be held on January 27, 2017. Additional Council meetings in 2017 will be held on May 26 and September 1.

II. INTRODUCTION TO THE PILOT CENTERS PROGRAM FOR PRECISION DISEASE MODELING

Oleg Mirochnitchenko, Ph.D., Program Director of the Division of Comparative Medicine (DCM), introduced the Pilot Centers Program for Precision Disease Modeling, a new initiative that addresses issues with existing models and assists new programs like PMI. He noted that recent advances in human genotyping allow significant information to be collected and stored, but this information must be interpreted and, for precision medicine, tailored to each patient's individual needs. Another recent technological advance is the use of clustered regularly interspaced short palindromic repeats (CRISPR) – associated nuclease, which allows previously difficult genetic engineering to be done rapidly and more easily. The next generation of precision animal models will improve the understanding of the relationship between gene and phenotype, allow better classification and testing of disease and genetic variations based on the underlying biological mechanisms, and improve the disease simulation process with recapitulation of molecular mechanisms.

The Pilot Centers Program was developed with a U54 mechanism; Dr. Mirochnitchenko explained that applicants are required to include processes for integrated data collection, a disease modeling unit, and a translational or co-clinical section. He noted that applicants had to have infrastructure already in place, because the intent of the grant was to fund integration of already existing substructures in a pipeline for development of the animal models.

Out of more than a dozen applications received for the program, three pilot centers were funded in the summer of 2015. Representatives from the three centers met in the spring of 2016 to discuss their experiences to that point and their plans for future collaboration. Dr. Mirochnitchenko elaborated on the two centers not represented at this meeting. The Jackson Center for Precision Genetics is located at the Jackson Lab in Maine, a well-known center for mouse biology. Dr. Mirochnitchenko commended their inclusion of a number of clinical collaborations and noted that this team addresses a wide variety of disease conditions, from classic Mendelian diseases to complex diseases. The pilot center at the Icahn School of Medicine at Mount Sinai in New York uses fly avatars and drug cocktails for high-throughput screening; the results of the initial screenings will be eventually confirmed in genetically engineered mice and mouse stem cell models to develop personalized patient treatments.

The third center funded was the Memorial Sloan Kettering Cancer Center (MSKCC) Pilot Center for Precision Disease Modeling in New York. Dr. Mirochnitchenko introduced Scott Lowe, Ph.D., Chair of the Geoffrey Beene Cancer Research Center at MSKCC.

III. MSKCC CENTER FOR PRECISION DISEASE MODELING

Dr. Lowe thanked the Council for the privilege of presenting the MSKCC pilot center. He described the rapidly advancing state of precision medicine: genomic information about human disease is being produced at an extraordinary pace, and a human genome can be sequenced in approximately 2 hours. To take advantage of the increasing body of knowledge on genetic variations between individuals, variation in mutations or diseases needs to be understood from a functional perspective. Predictive disease models are needed to interpret genetic information and develop improvements in patient care. The goal of the MSKCC pilot center is to facilitate an understanding of how genetic variation influences human disease and to develop preclinical models to test therapeutic strategies based on this understanding. MSKCC provides the infrastructure to help integrate existing knowledge, support the center's disease modeling units, and enable investigators to access resources and expertise. MSKCC's preexisting infrastructure, world-class researchers and collaborators, and long history of producing animal models of human disease have helped advance the pilot center. MSKCC also supports a mouse hospital and a viable tumor cell initiative to produce models using genetically annotated human tissue. A key aspect of the pilot center is the MSK-IMPACT™ (Integrated Mutation Profiling of Actionable Cancer Targets) test, a capture-based sequencing method developed by MSKCC that characterizes approximately 450 genes, both tumor-related and normal, from all cancer patients. This initiative provides both a pipeline to match patients with personalized therapies and a large amount of research data for the cancer community. Data from MSK-IMPACT™ is linked to a private server, cBioPortal, which is a portal for public data on mutational catalogs of different cancers, and all MSK-IMPACT™ data are clinically annotated.

The goals of the pilot center include building an infrastructure and a database management system that utilizes the available data from patients and animal models. The pilot center is structured around the Coordination Core, which includes the Genomics and Bioinformatics Core and the Preclinical and Co-clinical Core. The Genomics and Bioinformatics Core has generated a mouse version of the MSK-IMPACT™ panel to characterize murine tumors in a cost-effective and rapid way. The Preclinical and Co-clinical Core has improved upon preexisting technologies by using mice as surrogates for drug trials to anticipate or validate the drug targets and characterize how inhibiting a drug in the context of a tissue or tumor affects the animal. The center's mouse modeling unit has refined the site-directed recombination technologies (e.g., Cre/Lox and FLP/FRT) to design new mouse models of disease. Over the last year, the center has generated 12 new genetically engineered mouse models based on mouse embryonic stem cells (GEMM-ESC) and provided more than 1,000 animals for experimental studies.

Dr. Lowe described ways the center is using standard CRISPR technology in addition to newer procedures for gene repression (CRISPRi) and gene activation (CRISPRa) for gene expression and model somatic mutations in cancers or to produce chromosome rearrangements. CRISPRa can be used to create combinations of gene types to study gain and loss of function. The center has been using this method in studies of liver cancer, which is the second leading cause of cancer deaths in the world, yet it remains poorly understood. The timeline for mutating two different cancer genes in the liver is 2 to 3 years using standard methods, but with liver DNA editing it can be done in 1 to 2 months. He added that the human data from the MSK-IMPACT™ data supports the mouse models developed by the center.

Dr. Lowe then discussed MSKCC's Mouse Hospital, which mirrors the human cancer center; available functions include imaging, pharmacy activities, integrated pathology labs and bioinformatics programs, education and outreach, and mouse modeling of human disease. The Mouse Hospital can support preclinical studies to mirror treatment plans used for human patients, concepts based on genetics and phenotypes can be translated into clinical reality, and the efficacy and toxicology of planned treatments can be studied. Dr. Lowe summarized the pipeline for patient-derived xenograft (PDX) production and highlighted a new treatment strategy for gastric cancer.

Dr. Lowe briefly described several pilot projects at MSKCC using mouse models of human diseases: a study of the role of mutations in epigenetic modifiers in acute myeloid lymphoma (AML); a study of RTEL1 mutations in Hoyeraal Hreidarsson Syndrome; and development of models for advanced colorectal cancer (CRC) *in vivo*. In all three studies, researchers demonstrated that the mouse models recapitulate human disease. Dr. Lowe noted that the funding strategy will support salaries in key positions to subsidize user costs, a modular method that supports use by anyone, not just the disease modeling units. MSKCC's collaboration program with supporting institutions also has been expanded to support this project. Dr. Lowe thanked the Council for supporting the efforts of the pilot center.

Discussion Highlights

- The intent of the pilot center is to create the infrastructure to support any proposed study regardless of topic area; the key features at MSKCC are the MSK-IMPACT databases and the Mouse Hospital. These systems are flexible and can be used to study issues beyond cancer.

- Patients at MSKCC are sequenced both after initial diagnosis and after any relapses.

  Mosaicism in mice produced from ES cells harboring multiple alleles is not a concern for cancer studies and mice produced following blastocyst injection are used without further strain intercrossing.

- Though clinicians may be hesitant to use a targeted treatment rather than the standard of care, a system in place at MSKCC automatically generates an email to the oncologist if a druggable, actionable mutation is identified in a patient. The intent is to encourage oncologists to be proactive about clinical trials, and as more successes occur and the evidence base is strengthened, these treatments can be incorporated sooner.

- The most fundamental function provided by this mechanism is coordination, thanks to MSKCC's vision. The teams involved interact regularly and receive strong input from the Functional Genomics Initiative, the external advisory board, and the oversight committee.

- Interface with industry has not yet been explored but could offer promising insight and opportunities for collaboration.

IV. CONCEPT CLEARANCE: HUMAN TISSUE AND ORGAN RESEARCH RESOURCE

Stephanie Murphy, V.M.D., Ph.D., Director, DCM, presented a proposal for continued support of the Human Tissue and Organ Research Resource (HTORR) utilizing a Limited Competition U42 mechanism. The HTORR U42 grant was administered by the National Center for Research Resources for more than 20 years before being reassigned to ORIP in 2011. During the current project period of September 2013 to June 2018, six NIH Institutes and Centers (ICs) have partnered with ORIP to co-fund HTORR, with the National Institute of Mental Health providing administrative supplements in fiscal year (FY) 2015 and FY 2016. As part of the National Disease Research Interchange (NDRI), HTORR provides diseased and normal human tissues and organs to support active ongoing research projects in many scientific disciplines such as eye diseases, rare diseases, and HIV/AIDS. The ICs that have indicated interest in partnering with ORIP to co-fund HTORR for the next proposed project period are the National Eye Institute; National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institute of Diabetes and Digestive and Kidney Diseases; and National Institute of Arthritis, and Musculoskeletal and Skin Diseases; the National Center for Advancing Translational Sciences will not be continuing its support. The average total cost for the base grant award is approximately $1.36 million (M) per year; ORIP contributes approximately 45 percent of the total cost. The HTORR initiative as a trans-NIH activity is clearly shown by the number of tissues shipped by HTORR over the past 5 program years to investigators supported by a variety NIH ICs, including both IC co-funders and non-funders . HTORR was referenced as a provider of biospecimens in 152 publications in 2015; the five most frequently referenced topics—ocular research, basic science, musculoskeletal research, cancer research, and respiratory research—account for approximately 70 percent of the publications. The variety of scientific fields acknowledging use of HTORR demonstrates the trans-NIH nature of HTORR's activities and interactions.

Discussion Highlights

- Some cost recovery is possible for projects that are part of NDRI but not supported by the grant.

- HTORR is an interchange rather than a tissue bank, so the procedures are flexible. Investigators work with HTORR to develop the protocols for each individual project and determine the best plan in collaboration with HTORR's procurement network. This can be an impetus for expanding the procurement network if a project's needs cannot be met with existing resources.

- Dr. Murphy considers HTORR to be successful because it meets the needs of the ICs. An additional demonstration of success is the increase in the number of projects and areas supported over time.

- The disorders supported by HTORR vary each year and may not always reflect the burden of disease. The ability to add new members to the network will affect the distribution of diseases over time. HTORR also serves as a complement to other NDRI programs that focus on different tissues, such as the Common Fund Genotype-Tissue Expression (GTEx) program.

- ORIP's contribution to HTORR currently is about $600,000 yearly out of an annual ORIP budget of $280 M. If the Council decides not to continue funding this initiative through ORIP, another IC could assume a leadership role; however, the trans-NIH nature of HTORR is in line with ORIP's strategic plan. If approved, the next step would be to release a Funding Opportunity Announcement.

- Prospective ways of evaluating the program and determining whether it is meeting goals should be written into the request for applications.

Vote

A motion to approve "Human Tissue and Organ Research Resource" was forwarded and seconded. The motion passed unanimously.

V. NIH UPDATE

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH, presented on three topics: the NIH budget, efforts to enhance reproducibility and transparency of research findings, and the transitioning to a new administration. The $2 billion (B) increase in the NIH budget for FY 2016 allowed support for the highest number of Research Project Grants since 2003, including high-profile projects such as PMI, antimicrobial resistance, the BRAIN Initiative, and Alzheimer's disease research. The FY 2017 request includes an increase that will allow the NIH to continue its momentum on these projects. Targeted increases have been requested for the National Cancer Moonshot, PMI Cohort, and BRAIN Initiative; these items must be supported from funds designated as mandatory. The remainder of the budget request maintains the FY 2016 level, but only $1 B of that request will be drawn from mandatory funds. Although recent funding has supported significant research, the practical buying power of the NIH budget remains below its 1998 level. Dr. Tabak noted that although budget support is unpredictable in an election year, the NIH mission resonates with members of Congress on both sides of the aisle.

Dr. Tabak was asked how NIH funding compares to other budget items in the public consciousness, such as infrastructure. He explained that the NIH is one of the larger items in the discretionary budget, whereas items like roads are mandatory. He noted that the amount shown for FY 2017 is the amount requested in the President's budget. Although the anticipated percentage of successfully funded applicants appears slightly lower than FY 2016, variations reflect turnover in grant length—the average grant lasts about 4 years, but ending lengths are staggered, so a larger number of new applications can be funded in years when more projects end. Dr. Tabak was asked about the status of the FY 2017 budget request, and he commented that news reports suggest congressional leadership will request a continuing resolution into mid-December. He noted that the fiscal year begins on October 1, so a continuing resolution is needed to avoid a shutdown.

Dr. Tabak moved to the topic of reproducibility, which transcends all research fields and even has reached the pop culture consciousness. He emphasized that this is not an issue of misconduct by researchers; the NIH theorizes that a lot of reproducibility problems relate to deficiencies in experimental procedures and insufficient reporting in journal articles. Dr. Tabak showed publication reviews addressing these errors and suggested additional procedures and analyses that could be included to increase rigor. Council members questioned whether the suggested analyses were practical given the number of unknown variables that could have affected the study. Dr. Tabak emphasized that the most important adjustment to be made on the example study would be to include a sufficient number of animals, especially when the study in question is the antecedent to a human trial. Council members agreed that the study population should be a sufficient size but countered that budgets often do not increase to allow larger studies. The funding environment can be a challenge, and the investigators do their best science within these limitations. Dr. Tabak remarked that it is better to ask for more funding than to perform an underpowered study that may lead in the wrong direction. He noted that although resources often are scarce, lack of funds cannot be used as a justification for substandard science. The public conversation is critical to moving the field toward attaining the necessary support.

Dr. Tabak suggested that there is an overemphasis on p-values and statistical hypotheses, noting the prevalence of "p hacking," or reanalyzing the data in different ways until the desired results are shown. He emphasized that authors should report the rules for data collection prior to the study. Another recently illuminated problem in research is animal and cell studies that do not take sex differences into account. Not every study is obligated to review effects on both sexes, but every study should explain why only one sex was studied or scientifically demonstrate an equal response. Council members questioned the budget and infrastructure necessary to study twice as many animals and noted that, in practice, study sections often do not accept justifications for studying a single sex. Dr. Tabak thanked Council members for informing him that these explanations were not being accepted; he planned to discuss this issue with the Center for Scientific Review.

Another current issue is the lack of authentication for a large percentage of cell lines used by researchers. A study published on bioRxiv showed that 11 percent of cells studied were contaminated with *Mycoplasma*. NIH's efforts to combat this problem include raising community awareness and conducting workshops for researchers and journal editors. Many journals have endorsed principles designed to increase rigor, and these efforts are being supported by outside organizations, such as the American Statistical Association. NIH's Web portal includes modules for formal training in rigor and reproducibility; many ICs also are collaborating to develop additional training. NIH's application criteria have been revised to ensure that researchers have a solid scientific premise. Efforts are underway to increase the sharing of information, such as a pilot project involving PubMed Commons, which allows researchers to create a scientific dialogue around papers published on PubMed. Additionally, biological research is beginning to utilize prepublication servers, and most journals now accept submissions of papers that have been prepublished. Dr. Tabak also recommended collaborations with industry, which often must consider research from different perspectives than academia.

Dr. Tabak emphasized that the NIH understands the pressures investigators face and is working to increase stability. He referred to a commentary on the issue of reproducibility co-written with Francis S. Collins, M.D., Ph.D., Director of NIH, and published in *Nature* in 2014: "Efforts by the NIH alone will not be sufficient to effect real change in this unhealthy environment." He recommended that Council members stimulate discussion at their own institutions, promote rigorous training, and provide an example of transparency.

Dr. Tabak was asked how to measure improvement and reward rigorous studies; he recognized the tendency to laud flashy studies more than those that support their fields more incrementally and acknowledged that solutions have not yet been determined. A Council member pointed out that competition among journals can make higher standards a barrier to publication. Dr. Tabak responded that to support this effort, researchers must make the difficult decision to send their work to journals with appropriate standards and support applicants with a history of publishing at such journals. Council members commented that young investigators may be hesitant to use PubMed Commons to criticize the research of established scientists even when justified. Dr. Tabak described the example of such fields as psychology, which regularly invites discussion on published research and often results in additional publications with refined results. Council members questioned the feasibility of requesting more funding when budgets are always returned lower than the requested support; Dr. Tabak emphasized the importance of being assertive when the budget is scientifically justified. He noted that he will take the results of these discussions to other IC leaders to move the field in a relevant direction.

Dr. Tabak discussed the upcoming transition to the next presidential Administration. A new administration makes about 4,000 appointments, 1,000 of which require Senate confirmation; the only Presidentially-appointed positions at the NIH are the Director of NIH, who requires Senate confirmation, and the Director of NCI, who does not. The NIH thus has more stability than many agencies. The Partnership for Public Service is working to make the transition efficient and has helped both parties

agree on some guidelines. The current Administration has convened both a White House Transition Coordinating Council and an Agency Transition Directors Council. Transition leaders currently are selecting those who will review departments and agencies after the election.

Council members asked how to assuage fears that researchers' bodies of work would be discredited by an administration moving in a new direction. Dr. Tabak emphasized that science should not be political; the best way to ameliorate politicization is to engage policymakers and the general public with facts and explanations. Council members and Dr. Tabak agreed that both the NIH and the greater biomedical research community should continue to increase efforts to support and publicize rigor.

VI. CONCEPT CLEARANCE: EFFECTS OF LABORATORY CONDITIONS ON RIGOR OF EXPERIMENTAL PROTOCOLS AND REPRODUCIBILITY OF EXPERIMENTAL OUTCOMES

Malgorzata Klosek, Ph.D., Director, Division of Construction and Instruments (DCI), presented a proposal to study the effects of laboratory conditions on animal model research. The proposed concept is a collaboration between the DCI and the DCM and would combine their expertise in animal facilities and animal models. This concept would investigate the role of standard laboratory environmental conditions on the outcomes of animal model experiments. Environmental variations between institutions could be having unknown effects on experiments assumed to be standardized. Ideal applicants for the funds would be multidisciplinary research teams or cross-institutional collaborations.

Prospective discoveries include factors that need to be controlled in certain models and experiments, correlations between extrinsic factors and experimental outcomes, or the biology of the mechanisms involved in these outcomes. The study also would enhance rigor and reproducibility long term. The DCI could use new discoveries to determine any special tools that might be needed to correlate conditions between facilities and any factors to be considered in designing facilities to better meet research needs.

The proposed initiative would be funded with $6 M currently allocated to a G20 program; awards would be made for $250,000 in direct costs each year for up to 2 years, using a funding mechanism such as R24 or U24. The research would be exploratory rather than hypothesis-driven, and the output would include community-wide dissemination of results.

Discussion Highlights

- This proposal would utilize funds from a G20 program that likely will not continue into FY 2018. The budget for this proposal is not yet finalized; a workshop of experts could be convened to determine the most effective way to fund specific areas of study.

- Council members expressed concern that the proposal was not yet fully defined and recommended querying facilities that have published studies of environmental conditions—such as the mouse laboratories in Bar Harbor, Maine; Ann Arbor, Michigan; and San Antonio, Texas—to determine the best processes and study parameters.

- Dr. Klosek was asked whether individual facilities might operate under specific governing principles that would affect their inclusion in this study; she noted that the proposal would not issue new guidelines but would gather information about how the baseline guide for animal care is implemented differently. The intent is to inform the community of the potential for unintentional outcomes and encourage more detailed reporting on conditions.

- Council members did not conduct a formal vote on this proposal; the proposal will be refined based on the discussion and returned to the Council at a later date.

VII. 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).[1] 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 69 ORIP applications with requested first-year direct costs of $27,003,673. The Council also concurred with the review of 69 responsive Common Fund applications with first-year direct costs of $17,114,971 and the review of 152 responsive Environmental influences on Child Health Outcomes (ECHO) applications with first-year direct costs of $304,915,959.

VIII. COUNCIL OPERATING PROCEDURES

Ms. Kawazoe explained that the Council's operating procedures are reviewed and updated annually. She summarized this year's proposed changes, which were sent via email to Council members on August 26, 2016, including the addition of the ECHO program and the PMI Cohort program. The Council of Council's Operating Procedures document has been revised to reflect these changes, pending Council approval.

Vote

A motion to approve the changes to the Council's Operating Procedures was forwarded and seconded. The motion passed unanimously.

IX. CONCEPT CLEARANCE: LIMITED COMPETITION FOR VETERINARY K01 GRANTEES TO APPLY FOR R03 GRANTS

Dr. Murphy presented a concept designed to support biomedical researchers with veterinary degrees who have funding from ORIP for Special Emphasis Research Career Award (SERCA) K01 grants. These SERCA awards provide a mentored research experience that enables veterinarians to become independent investigators in comparative medicine, biomedical research, and translational sciences. R03 grants have recently been used by other ICs to supplement career development (K) grants during the last 2 years of the award; those who receive such grants may have greater success in obtaining R01 grants.

ORIP's strategic plan supports veterinary scientists in acquiring the skills needed to participate in biomedical research, which aligns with NIH's interest in expanding the physician scientist workforce. Participants from a 2015 workshop focused on One Health and the integration of veterinary scientists into

[1] 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.

biomedical research, and identified the need for support for veterinary scientists transitioning between K01 and R01 grants.

ORIP seeks to enhance the ability of its SERCA K01 recipients to conduct research as they transition to becoming independent researchers by developing their own R03 supplement program. The proposed initiative is intended to support short-term, limited, or preliminary projects, such as pilot studies, secondary analyses of existing data, or self-contained research projects. Researchers in the third or fourth year of a SERCA K01 award will be eligible; awardees who have successfully competed for an R01 or equivalent grant will be ineligible. This grant would include a budget of up to $150,000 in direct costs for 2 years. An evaluation by ORIP at the end of the fifth year of the program is planned. Dr. Murphy anticipated between nine and 12 eligible applicants each year and three to four successfully funded meritorious proposals per year. The first year of this program would require a commitment of $300,000 to $400,000; ongoing maintenance of the program would fall between $600,000 and $800,000 per year.

Discussion Highlights

- Council members expressed support for this concept as a method of easing the complex process of transitioning between career stages. It was noted that the community of veterinary researchers contributes important work and is frequently undervalued.

Vote

A motion to approve "Limited Competition for Veterinary K01 Grantees to Apply for R03 Grants" was forwarded and seconded. The motion passed unanimously.

X. COMMON FUND PLANNING UPDATES

Elizabeth L. Wilder, Ph.D., Director, OSC, introduced updates on Common Fund projects that were presented in preliminary form in January. These concepts have been refined but have not yet been funded; this is an opportunity for Council members to receive an update and provide feedback prior to making support decisions later this fall.

Transformative High Resolution Cryo-Electron Microscopy (CryoEM)

Jon Lorsch, Ph.D., Director, NIGMS, explained that recent advances in electron microscopy have allowed scientists to view biological structures at atomic resolutions and correct for blurring caused by small particles in motion. Despite these advances, the United States is falling behind many other areas of the world in providing full access to these technologies to its scientists. Most cryoEM equipment in the United States is owned by institutions or corporations that restrict access; many other countries support both small-scale and large-scale shared cryoEM facilities. A Request for Information released in June received overwhelming support for a proposed model to create national centers for shared cryoEM. Respondents also expressed support for adding cryo-electron tomography, additional training mechanisms, and improved data management to the proposed centers. Dr. Lorsch demonstrated the benefit to ICs by presenting recent discoveries that have been made using cryoEM—including the determination of the structure of HIV antibodies, Ebola antibodies, the Zika virus, and a potential cancer therapy target, all of which will assist researchers in progressing toward solutions to these conditions.

The proposal to create national centers would prevent the problems with economy of scale caused when individual institutions maintain restricted facilities. This technology requires a large investment for purchase and additional funds to maintain; shared usage would assuage these costs. The proposal would create three centers, including expertise and training, and each center would engage in high-throughput

data collection. The long-term plan is to transition support from the Common Fund to the ICs that have benefited.

The total budget in the first 3 years of the project would be approximately $144 M, and a small infusion in 2017 would help this proposal advance before individual institutions begin to purchase equipment. Dr. Lorsch explained that there are no true open-access cryoEM machines in the United States now; there are approximately 15 privately owned machines and another 10 on order at individual institutions. If institutions were amenable to transitioning their existing centers into open access centers, the proposed model for this project would be able to support that effort; Council members offered to liaise with institutional contacts and help publicize the proposal. In addition, Council members supported outreach to and engagement with the community and recommended additional refinements, including developing a clear definition of "open access," choosing facility managers with the appropriate skills, and collaborating with experts in related fields, such as crystallography.

Human Biomolecular Atlas Project (HuBMAP)

Robert Carter, M.D., Deputy Director, NIAMS, presented an update on HuBMAP. He explained that for any given cell *in situ*, the best process for understanding its purpose is to understand how it relates to other cells, and applying the same principles at the tissue level can increase the understanding of principles that operate across tissues. A multi-layered understanding of such interactions also increases the richness of data available about each particular cell. The HuBMAP team has been researching related efforts currently underway at the NIH, but, except for cancer and blood cells, other ICs rarely study problems at the single-cell level, and HuBMAP is the only project to study spatial resolution across human tissues. Some programs are working on initiatives, such as protein analysis studies, which offer opportunities to develop synergistic collaborations with HuBMAP. Single-cell study technology can illuminate not only known cells, but also types of cells that are less studied. Current techniques, such as fluorescence *in situ* hybridization (FISH), allow enough resolution to study transcription factors, which is critical to understanding what is occurring in a cell. Another new technology involves applying mass spectrometry to flow cytometry; heavy metal ions, which can be individually distinguished by mass spectrometry, can be conjugated to antibody probes to provide greater resolution and less overlap in imaging.

The proposed goals for the HuBMAP project include understanding the principles underlying the organization of cells across tissues and the ways these cells communicate. This will increase the understanding of individual variation between cells, between people, over the lifespan, and in various diseases. Defining the pipeline will be critical for ensuring cells are delivered, preserved, and analyzed appropriately. The first phase in this process will attempt to understand these functions in normal, healthy people. When this baseline is established, researchers can move to the second phase and study single-cell functions across the lifespan. A final goal is to learn how to manipulate human tissues in vitro. Dr. Carter noted that the intent of the project is not to seek or request specific tissues but to study those tissues that researchers provide. The next steps for this project include defining and refining boundaries so that a practical number of tissues are studied, continuing to develop synergies with related projects, and determining best practices. The budget includes $21 M per year in the first phase and $38 M per year in the second phase.

Dr. Carter was asked whether the profusion of cataloguing efforts at the NIH is a better strategy than asking a discrete biological question. He responded that these databases have already produced a large amount of information that cannot be produced otherwise, many publications that demonstrate a technique but do not answer a specific question nonetheless can open up a field, and little information is available on the single-cell level for normal, healthy function. He emphasized the fundamental nature of this missing knowledge area and added that small Institutes, such as NIAMS, generally cannot perform

large cataloguing studies without collaborations with other groups. Council members encouraged the study of dynamics in addition to static tissues and asked how Dr. Carter would engage the research community in this effort and define a specific set of priorities for such a broad study. He explained that a group of IC directors will meet in an upcoming session, and he hopes this meeting will determine some strategies for prioritization. Dr. Wilder added that prioritization often can be refined after the award is received, according to the expertise of the funded investigators.

Mechanisms of Fatigue

Carlos Blanco, M.D., Ph.D., Director, Division of Epidemiology, Services, and Prevention Research, NIDA, updated the Council on a proposed study of fatigue. Fatigue is pervasive—it can be experienced both by healthy individuals and as a symptom in a wide variety of conditions—yet it is not well understood, and scientists cannot agree on a specific definition. The field also lacks consensus on the function of sleep in fatigue—some contend that fatigue is eased by sleep, but others define some types of fatigue by the inability to improve with rest. The mechanisms of fatigue also are not yet well understood. Dr. Blanco noted that less than one-third of the $163 M awarded to study fatigue in recent years has funded studies of its mechanisms. Because fatigue is prevalent across many conditions, there is an opportunity for collaboration across diverse ICs. Fatigue researchers advised the team co-lead by Dr. Blanco and Dr. Vicky Whittemore, and co-chaired by Drs. Nora Volkow and Walter Koroshetz, that they frequently work in silos. Goals for this project include correlation of the subjective experience of fatigue with objective factors and conceptualization of a taxonomy of fatigue to study the differences between physical fatigue, emotional fatigue, and intellectual fatigue. Dr. Blanco proposed two workshops to be held in FY 2017. The first workshop would develop the taxonomy of fatigue and define the metrics of study, and the second workshop would evaluate the relationship between sleep and fatigue and identify important energetics, metabolomics, and lymphatics. The intent of these workshops is to refine the field and help the team develop a specific proposal to move this project forward.

XI. REPORT FROM THE SEXUAL AND GENDER MINORITY RESEARCH WORKING GROUP

Kimberly K. Leslie, M.D., University of Iowa Hospitals and Clinics and Member of the Council, provided an update on the Sexual and Gender Minority Research Working Group of the Council of Councils. The phrase "sexual and gender minority" (SGM) encompasses gay, lesbian, bisexual, and transgender (LGBT) populations, as well as those whose sexual orientation, gender identity and expressions, or reproductive development varies from traditional societal, cultural, or physiological norms—in other words, the LGBT and intersex or disorders of sexual development (DSD) populations. Research to support these populations is critical because they experience significant health disparities. In states with a large amount of anti-gay bias, members of these populations have a life expectancy 12 years shorter than average, affected by such factors as stress, cardiovascular disease, and an increased incidence of cancer; these minorities also experience greater rates of homelessness, suicide, violence, harassment, and alcohol dependency. Of the studies being conducted with this population, very few do not relate to HIV/AIDS. Dr. Leslie commented on the fundamental role that determination of sex plays in the way an individual is raised and experiences the world, and she noted that little consensus exists on the best methods for assisting intersex individuals. Despite the significant health disparities, no single NIH Institute is interested in the study of SGM populations; this population is not included in the portfolio of the National Institute of Minority Health and Health Disparities, which Dr. Leslie considers a missed opportunity.

The Sexual and Gender Minority Research Office (SGMRO), led by Dr. Karen Parker, was established in 2015. The office budget is about $700,000 which does not allow the support of many studies; Dr. Leslie

expressed the hope that the Council would support future efforts to partner with other Institutes and Centers (IC) and lead to presentation of specific concepts. The role of the SGMRO is to coordinate SGM research across the NIH, represent NIH SGM research at conferences and events, collaborations with other ICs, and work to leverage resources and/or develop initiatives to support SGM research. Dr. Leslie emphasized that the Council hears about many studies at the second level, but this Working Group is the Council's creation and presents an opportunity to be creative and proactive. The Working Group met the day before Council to discuss ideas, and Dr. Tabak has been very supportive; Dr. Leslie planned to bring strategic plans and recommendations to the Council in the future.

Discussion Highlights

- Council members suggested reviewing other NIH offices that started as small entities, such as the Office of Research on Women's Health, and investigating grants for the development of future researchers. The SGMRO's strategic plan includes objectives to support young researchers in SGM studies, and Dr. Leslie recognized the importance of such programs as K12 and T32.

- Many advocacy organizations are focused on SGM populations, but few include a significant health research component.

- Council members recommended NIH Institutes as potential collaborators, including the National Institute of Minority Health and Health Disparities and the National Institute of Mental Health, as well as groups outside the NIH, such as the Division of Adolescent and School Health at the Centers for Disease Control and Prevention.

- Although visibility of SGM populations has increased on college campuses, many students who proceed to medical and graduate schools are unable to express their identities as publicly because upper-level institutions have focused less on this issue. Dr. J.P. Sanchez, one of the SGM Working Group members, emphasized the need for developing a supportive culture and mentorship throughout students' and trainees' careers.

XII. PRECISION MEDICINE INITIATIVE® (PMI) COHORT PROGRAM UPDATE

Mr. Eric Dishman, Director of the PMI Cohort Program, provided an update on three components of the Program: the progress in building an interdisciplinary platform team; the testing process for that platform; and the preparations for maintaining this effort in the long term. The challenge of developing a platform team is to utilize each award and team member as part of a whole, rather than as individual entities. The platform team must deliver an engaged and diverse volunteer force and support them for many years; they also must develop a database that can be used by diverse fields and advance the field of precision medicine for the long term. Mr. Dishman commented on the challenge of translating user-centered design methods from his industry experience to this effort. He described the concept of "landing zones," which allows the team to use the same resources to determine whether to aim for minimum, goal, or stretch goal landing zones.

The PMI Cohort Program involves around 33 organizations and 15 government agencies encompassing healthcare provider organizations (regional medical centers, health centers, and Veterans Administration medical centers); and the Data and Research Support Center and the Participant Technologies Center, which are building the back-end and front-end infrastructures, respectively. The Participant Technologies Center also is managing the direct volunteer enrollment, engagement and retention. The program is currently hiring the core senior leadership team and building a network of community partners, and they also are developing plans for the transition of administrations.

Testing has begun of the ecology model—the user-experienced design of interfaces - —and the draft consent language. Engagement and enrollment strategies for volunteers from diverse communities also are under development. The program will launch incrementally, with some components ready in late fall or early winter.

The program will conduct workshops with NIH Institutes and Centers around key bodies of knowledge to determine the platform releases for the next 5 to 10 years, so that each new release can further advance the scientific use of the cohort across a broad range of disciplines.

Discussion Highlights

- Mr. Dishman emphasized the plan to release portions of the platform incrementally; initial release may increase various fields of knowledge by relatively small amounts, but each subsequent revision will increase the knowledge gained in specific domains as the platform grows.

- The platform will be designed to support not only Tier 1 efforts but also community-level work, such as precision medicine work at community colleges or citizen science projects.

- Many industry groups have expressed interest in supporting the program; this may present logistical challenges, but these opportunities can be explored after the program has been developed further.

- The rapid pace and cross-agency efforts have been strongly supported by the current Administration, including the President himself. Members of councils or Council of Councils could help publicize the efforts of the program.

XIII. RETIRING COUNCIL MEMBER PERSPECTIVES

Drs. Belfort, Cuervo, Gierasch, Holmes, and Kenyon reflected on their experiences serving on the Council of Councils, offered suggestions, and provided advice to new Council members.

Dr. Holmes expressed appreciation for the single-day Council meetings and the interdisciplinary nature of the topics reviewed. He commented that presentations were succinct but inclusive of large amounts of science. The meetings are relatively formal, and the Council is very well-organized. Dr. Holmes disagreed with the Council's reputation as "rubber-stampers" and appreciated that time was allowed for discussion and Council members were open to negotiation. He encouraged future members to suggest topics for discussion and urged the NIH to utilize former members to expand the audience for the projects discussed. He also recommended that presenters emphasize the practical relevance of their research by providing case studies or identifying problems to be solved.

Dr. Belfort appreciated that Council meetings provided an overview of diverse NIH activities. She noted that the experience had less texture than she had hoped; applications that are contentious tend to generate a more thorough dialogue. She encouraged more spirited discussion, perhaps by extending the closed session.

Dr. Cuervo noted that she is always excited to return to her laboratory and share what she has learned at Council meetings. She commented that every investigator should pass through the Council at some point to appreciate the efforts of the NIH, but she wished Council members could take a more active role. She recommended for Common Fund topics providing more context for concepts to answer questions like why now, why is this topic being proposed, and suggested that new members advocate for changes they would like made to the concepts.

Dr. Gierasch noted the difference between her expectations upon accepting the invitation to join the Council and the actual content of the meetings. She added that the orientation for the Council included an excess of acronyms. She appreciated the bird's eye view of NIH activities, but she occasionally felt underutilized and that she sometimes needed a big picture context for topics. She suggested a mentoring system that could help alleviate the first few sessions' confusion for new members.

Dr. Kenyon commented on the professionalism of the staff with admiration and respect, and she concurred with those who said they would have liked to contribute more. She also noted that more integration is needed between translational science research and commercialization.

XIV. CLOSING REMARKS

Ms. Kawazoe thanked the Council members and speakers for their contributions at this meeting. She reminded the members that the next Council meeting will be held on January 27, 2017.

XV. ADJOURNMENT

Ms. Kawazoe adjourned the meeting at 3:44 p.m. on September 9, 2016.

XVI. CERTIFICATION

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

/Robin I . Kawazoe/
Robin I. Kawazoe
Chair, NIH Council of Councils
Deputy Director, DPCPSI, OD, NIH

10-17-2016
Date

/Franziska B. Grieder, D.V.M., Ph.D./
Franziska B. Grieder, D.V.M., Ph.D.
Director, ORIP, DPCPSI, OD, NIH
Deputy Director, DPCPSI, OD, NIH

10-17-2016
Date