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
January 29, 2016

Draft 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, January 29, 2016, in Building 31, Conference Room 10, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson welcomed new members Mr. Jorge Contreras, Ms. Nsedu Obot Witherspoon, Ms. Gail Yokote, and Drs. Eric Boerwinkle, Melissa Brown, Joseph Buckwalter, Jonathan Epstein, David Holtzman, John Postlethwait, and Leslie Winston. He noted that Drs. Boerwinkle, Norma Sue Kenyon, Guillermina Lozano, and Keith Reimann were unable to attend the day's meeting. 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 and described changes in the DPCPSI, including the establishment of two offices (Sexual and Gender Minority Research Office and Tribal Health Research Office) and the formation of three Council of Councils Working Groups (Sexual and Gender Minority Research, Precision Medicine Initiative® Cohort Program Advisory Panel, and Environmental Influences on Child Health Outcomes (ECHO) External Scientific Board). He referred Council members to the fourth Director's Report, included in their meeting books, which highlights upcoming meetings, funding opportunity announcements (FOAs), and other DPCPSI activities of interest.

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, OD, NIH
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
Joseph Buckwalter, M.D., University of Iowa College of Medicine, Iowa City, IA
Molly Carnes, M.D., M.S., University of Wisconsin–Madison, Madison, WI
Jorge Contreras, J.D., University of Utah, Salt Lake City, UT

Ana M. Cuervo, M.D., Ph.D., Albert Einstein College of Medicine, Bronx, NY
Jonathan Epstein, M.D., University of Pennsylvania School of Medicine, 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
David Holtzman, M.D., Washington University School of Medicine, St. Louis, MO
Terry L. Jernigan, Ph.D., University of California, San Diego, La Jolla, CA
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
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
J. Leslie Winston, 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

Eric Boerwinkle, Ph.D., The University of Texas Health Science Center at Houston, Houston, TX
Norma Sue Kenyon, Ph.D., University of Miami School of Medicine, Miami, FL
Guillermina Lozano, Ph.D., The University of Texas MD Anderson Cancer Center, Houston, TX
Keith A. Reimann, D.V.M., University of Massachusetts Medical School, Boston, MA

2. Liaisons

Janine A. Clayton, M.D., Director, Office of Research on Women's Health (ORWH), DPCPSI
Robert W. Eisinger, Ph.D., Acting Director, Office of AIDS Research (OAR), DPCPSI
Abby Ershow, Ph.D. (representing Paul M. Coates, Ph.D., Director, Office of Dietary Supplements (ODS), ODP, DPCPSI
David M. Murray, Ph.D., Director, Office of Disease Prevention (ODP), DPCPSI, OD
William Riley, Ph.D., Director, Office of Behavioral and Social Sciences Research (OBSSR)
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

Josephine Briggs, M.D., Director, National Center for Complementary and Integrative Health, and Interim Director, Precision Medicine Initiative® Cohort Program, NIH
Franziska Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs, DPCPSI
Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, NIH
Jon Lorsch, Ph.D., Director, National Institute of General Medical Sciences (NIGMS), NIH

Terry Magnuson, Ph.D., University of North Carolina at Chapel Hill, School of Medicine
Karen Parker, Ph.D., Public Health Advisor, DPCPSI
Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH
Elizabeth L. Wilder, Ph.D., Director, OSC, DPCPSI

5. 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. 5Meeting Procedures

Dr. Grieder reviewed the following:

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

- v 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.

- v 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 December 24, 2015.

- v Minutes from the September 1, 2015, meeting have been published on the DPCPSI website. The minutes from this meeting also will be published there.

C. 5Future Meeting Dates

The next Council meeting will be held on May 20, 2016. The other Council meeting in 2016 will be held on September 9.

II. NIH UPDATE

Dr. Tabak provided an update of NIH priorities and initiatives, including the budget, the NIH-Wide Strategic Plan, and the Environmental Influences on Child Health Outcomes (ECHO) program. Dr. Tabak said that the NIH experienced a good year in terms of its budget because Congress appropriated the first significant funding increase to the NIH in many years. He noted, however, that in terms of real dollars, the budget has not yet returned to the high level of the 1998 index year.

Dr. Tabak reviewed the elements of the NIH-Wide Strategic Plan, which articulates the highest trans-NIH priorities and how to achieve them. The strategic plan, which will be formally updated every five years, will continue to be refined throughout its lifecycle. It does not describe all of the many important or planned NIH activities, nor does it address priorities of the individual NIH Institutes, Centers, and Offices (ICOs), since each has its own strategic plan. The NIH-Wide Strategic Plan was developed in extensive consultation with NIH leadership and an NIH Working Group with ICO representatives, as well as public presentations to and feedback from the Advisory Committee to the NIH Director (ACD). Public input was obtained through multiple venues, including a request for information (RFI), three interactive webinars

facilitated by ACD members, and presentations to and feedback from the Department of Health and Human Services (HHS) and 20 National Institute and Center Advisory Councils. The plan was presented to the ACD on December 10 and transmitted to Congress and released to the public in mid-December 2015.

Dr. Tabak reflected on the unique moment of opportunity present in biomedical research, fueled by advances in technology, increased molecular knowledge, and interdisciplinary approaches to problem solving. The strategic plan aims to capitalize on this opportunity through four objectives. The first objective advances opportunities in biomedical research. Examples include new tool development for cell biology (e.g., structured illumination microscopy), establishment of the Interagency Pain Research Coordinating Committee to better understand pain and improve pain-related treatment, and the Precision Medicine Initiative® Cohort of 1 million U.S. volunteers to develop prevention and screening strategies tailored to individuals across the lifespan. Gene-editing technologies, better vaccines, and a translational timeline are additional opportunities that will advance biomedical research. Other objectives are to set priorities and enhance stewardship, including through the transparency of decision making, considering the value of eradicating a disease (i.e., HIV/AIDS and the recent review of research priorities), growing partnerships such as the Human Heredity and Health in Africa Consortium, enhancing the diversity of the NIH-funded workforce, and policies to ensure rigor and reproducibility of research (i.e., data sharing for NIH-funded clinical trials). Another objective is to excel as a Federal science agency by managing for results, such as by developing a relative citation ratio (RCR), which provides an alternative metric to the common journal impact factors used to identify influential papers.

Implementation of the strategic plan should have notable outcomes, and Dr. Tabak shared several predictions for 2020. These include that many thousands of cancer patients will experience enhanced survival from application of precision medicine. NIH-supported research will identify effective tailored behavioral and social interventions to promote health and prevent illness in populations that experience health disparities. NIH-supported clinical trials will show that at least a half-dozen interventions thought to be clinically beneficial actually have no value. In addition, the application of certain mobile health technologies will provide rigorous evidence for their use in enhancing health promotion and disease prevention. Another prediction is that the NIH will be known as the model agency for applying the scientific method to itself—for learning and implementing, in a rigorous way, how best to support biomedical research.

Dr. Tabak described the ECHO Program, which aims to investigate the longitudinal impact of pre-, peri-, and postnatal environmental exposures on pediatric development and health outcomes with high public health impact by leveraging extant cohorts and other available resources. Core elements to be collected from all participants include demographics, typical early health and development descriptors (e.g., microbiome), genetic influences on early childhood health and development (e.g., epigenetics), and environmental exposures (e.g., behavioral, biological, chemical, social), as well as patient-/person-(parent and child) reported outcomes (PROs). Pediatric health outcome focus areas are: upper and lower airway; obesity; pre-, peri-, and postnatal outcomes; and neurodevelopment. There is an additional opportunity to create an Institutional Development Award (IDeA) States Pediatric Clinical Trials Network to address access gaps for rural and medically underserved children through a national network for pediatric research embedded at IDeA locations and to link existing IDeA state centers with experts in clinical trials.

ECHO could address a variety of research topics, such as the specific relative contributions of genetic and environmental influences on child health, factors that render individuals or populations subjected to an exposure as either resilient or susceptible to disease, inflection points at which the body's normal physiologic homeostasis becomes dysregulated, and molecular and behavioral mechanisms involved in maintaining a healthy weight across the lifespan.

ECHO Program elements include the extant pediatric cohorts; a Coordinating Center; a Data Analysis Center; a PRO core leveraging an existing resource on pediatric patient-reported outcomes; a Children's Health Exposure Analysis Resource core, which is a standardized analytic core to measure biological exposure; a genetics core; and an IDeA States Pediatric Clinical Trials Network, including IDeA clinical sites and an IDeA Data Coordinating and Operations Center. FOAs for these elements were released on December 7, 2015.

Dr. Tabak stated that extant cohorts may include cohorts initiated in pregnancy or postpartum that continue to follow offspring outcomes; those cohorts that ended data collection on pregnant women and their offspring, but can demonstrate the capability to re-contact participants; and those cohorts that are currently recruiting and/or assessing pregnant or postpartum women and their offspring. The combined cohort size is anticipated to include 50,000 subjects and will encompass retrospective data analyses and prospective data collection in two phases. He described responsibilities of the Centers and cores, as well as the IDeA States Pediatric Clinical Trials Network, which will prioritize research investigating the four ECHO Focus Areas and have representatives on ECHO Steering Committee and subcommittees.

Dr. Tabak reviewed the structure and governance proposed for ECHO. The ECHO External Scientific Board will be a Working Group of the Council of Councils and provide recommendations for the Program Director. The Board's reports will be reviewed by the Council of Councils, which will perform concept clearance and secondary review for ECHO programs. Applications for ECHO are due by April 15, 2016, with peer review of applications scheduled for Summer 2016 and Council review completed in September 2016.

Discussion Highlights

- ‡ The strategic plan was requested by Congress and has been well received. Dr. Tabak was ‡ recognized for his role in leading a vision for the plan. ‡

- ‡ The ECHO program will measure the effect of genetic factors and environmental exposures on diabetes, obesity, and physical aspects that impact health and vitality—and ultimately, the longevity—of the child. The NIH uses the term "environment" in a broad way, and applicants may submit creative proposals, such as linking childhood exposures to such outcomes as academic or professional achievement.

- ‡ ECHO focuses on the earliest inputs into subsequent health outcomes, with an emphasis on cohorts from pregnancy to age 5. Cohorts involving older children are acceptable if they are able to answer the research questions.

- ‡ Dr. Tabak acknowledged the limitations that may arise from focusing a large research program on a specific age bracket but noted the importance of supporting a feasible and successful research program that could provide results.

- ‡ The fiscal year (FY) 2016 budget for the ECHO program is approximately $165 million and includes funding for the National Children's Study archives to ensure that biospecimen data are made available.

- ‡ The ECHO program could leverage the Precision Medicine Initiative (PMI) as a complementary activity for its proposed biobanking efforts and other components. A hallmark of ECHO will be to leverage existing resources—such as data analytics, data coordination, and genomics core components—in novel ways that dramatically enhance the capacity to answer challenging questions.

- The ECHO program will not involve an intervention arm in its first stage. ...

III. CREATION OF SEXUAL AND GENDER MINORITY RESEARCH OFFICE IN DPCPSI

Dr. Karen L. Parker, from the Sexual and Gender Minority Research Office (SGMRO), DPCPSI, described sexual and gender minority (SGM) research activities at the NIH. Dr. Parker explained that SGM includes those whose sexual orientations and gender identifies or reproductive development vary from traditional, societal, or cultural norms, including lesbian, gay, bisexual, transgender (LGBT), and others. Recognizing contemporary health disparities based on sexual orientation and gender identity, the Institute of Medicine (IOM) published the *Health of Lesbian, Gay, Bisexual, and Transgender Report* in 2011. The IOM report highlighted the need for research on demographics, social influences, inequities in health care, interventions, and transgender-specific health needs. The report was developed under four overarching frameworks, including intersectionality. Because racial, ethnic, socioeconomic, and geographic factors influence the health of SGM populations within the context of diversity, it is important to consider these issues in research. The report recommended that HHS collect sexual orientation and gender identity data and that the NIH implement a research agenda, develop standardized gender identity measures, support methodological research, and develop a research training approach to strengthen LGBT health.

The NIH established the LGBT Research Coordinating Committee (RCC) in March 2011 to begin addressing the IOM report's recommendations; this committee had a time-limited charge. In 2013, the RCC was re-convened as a standing trans-NIH committee. At that time, the committee chose to include intersex conditions in its areas of consideration and changed its name to the LGBTI (lesbian, gay, bisexual, transgender, and intersex) RCC. The RCC worked to facilitate and develop relevant activities across the NIH and with other federal agencies and perform portfolio analyses of NIH-funded LGBTI health research for FY 2010 and FY 2012. The portfolio analyses found that little research was focused on the particular health needs of distinct SGM subgroups and that, although many opportunities existed for research and training programs, research in these populations presents challenges in methodological approaches and data collection. The analysis revealed that three ICOs—the National Institute of Mental Health, the National Institute for Child Health and Human Development, and the National Institute on Drug Abuse—were funding the majority (74%) of the research in the area. In addition, approximately three-quarters of the research work was related to HIV/AIDS. Nearly 70 percent of applications relevant to LGBTI were submitted to non-LGBTI-specific FOAs. In 2015, the RCC changed its name to the Sexual and Gender Minority RCC, in order to be more inclusive of other populations.

The NIH used the findings from the portfolio analyses and feedback from intramural and extramural community stakeholders, as well as from the public, to develop a strategic plan to advance research on the health and well-being of SGM populations. The strategic plan's goals are to expand the knowledge base of SGM health and well-being through NIH-supported research; remove barriers to planning, conducting, and reporting such research; strengthen the community of scholars conducting SGM-relevant research; and evaluate progress on advancing SGM research. In 2015, NIH established the Sexual & Gender Minority Research Office (SGMRO), with the specific aims to coordinate SGM health research across the NIH, convene conferences to inform priority-setting and research activities, collaborate with ICOs, manage information dissemination about relevant research, and leverage resources and develop initiatives to support SGM health research. Dr. Parker described FOAs, including administrative supplements to be awarded in the summer of 2016, as well as requests for applications (RFAs) for research on disorders of sex development, behavioral interventions to prevent HIV in adolescent men who have sex with men, and youth and young adults living with or at high risk for acquiring HIV. She stated that the next steps are to

update the portfolio analysis with 2015 data, reconvene the SGM RCC with an updated charge, explore new opportunities for research collaborations, and implement the goals of the strategic plan.

Dr. Anderson described the charges to the SGM RCC and the Council of Councils SGM Working Group. The SGM RCC will provide a trans-NIH forum for discussing the diverse health research issues of SGM communities and serve as a catalyst for developing additional research and research training initiatives in this area. The Working Group will advise the Council on DPCPSI activities that relate to SGM research and SGMRO activities. The Working Group also will provide scientific expertise and advice to the Council on opportunities for trans-NIH research collaborations, as well as strategies to enhance the number of SGM researchers, optimize outreach to SGM researcher and stakeholder communities, and identify priorities for the most needed and promising areas of SGM research. Dr. Anderson invited Council members to indicate their interest in serving on the Working Group.

Discussion Highlights

- † Policy research is relevant for the SGM field, such as the effect of same-sex marriage policies on health care and access to health care, particularly for SGM populations who often do not have a regular health care provider.

- † The NIH Fogarty International Center is providing funding in the international arena for research on transgender populations.

- † Self-identification among the LGBTI community is a complicated issue, such as the distinction between sexual orientation and gender identity questions, or an orientation question in which a male indicates "heterosexual" but affirms sexual relations with both men and women. The IOM report recognized this as a key area for continued research.

- † Ten of the 17 ICOs participating in the administrative supplements program received applications, with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) receiving the highest number.

IV. OVERVIEW OF THE PRECISION MEDICINE INITIATIVE® COHORT PROGRAM AND THE COUNCIL'S ROLE IN OVERSEEING THE COHORT PROGRAM ADVISORY PANEL

Drs. Kathy Hudson, Deputy Director for Science, Outreach, and Policy, NIH, and Josephine Briggs, Director of the National Center for Complementary and Integrative Health and Interim Director of the Precision Medicine Initiative (PMI) Cohort Program, presented the NIH's current vision of and progress toward establishing the PMI Cohort Program. President Barack Obama introduced the concept in his January 2015 State of the Union address, and $200 million in appropriations were provided in the FY 2016 budget, of which $130 M were for the Cohort Program.

Advances in genomic analysis, electronic health records, and mobile health technologies have made it possible to consider a cohort study as large as the PMI. The core values of the PMI include opening participation to all interested individuals; representing the rich diversity of America; participants be considered partners in all phases of the program, not "subjects"; giving participants access to study information and data about themselves; ensuring data are broadly accessible for research purposes; and adhering to privacy principles and security protocols. Finally, the PMI is expected to be a catalyst for progressive research programs and policies.

In March 2015, NIH Director Dr. Francis Collins formed the PMI Working Group of the Advisory Committee to the Director (ACD) to develop a blueprint for the PMI Cohort Program. The Working Group provided the following recommendations for assembling the PMI cohort: (1) Recruit at least 1 million volunteers who broadly reflect American diversity; (2) establish a longitudinal cohort with continuing participant interactions; (3) enroll participants both directly and through referrals from health care provider organizations (HPO), and federally qualified health centers (FQHC); and (4) ensure substantial participant engagement in the development, implementation, and governance of the Cohort Program.

Dr. Briggs provided an overview of the implementation plan for the Cohort Program and introduced the broad NIH governance model, which includes the Council of Councils. Dr. William Riley, Director, Office of Behavioral and Social Sciences Research, has been recruited to serve as interim deputy director.

The initiative issued six FOAs in late 2015, including for the Coordinating Center, HPO Enrollment Centers, the Biobank, and the Participant Technologies Center; reviews are underway for pilot programs. The HPOs are being asked to recruit 10,000 enrollees in Year 1, and as many as 50,000 direct volunteers are expected in the first year; the projection is to have 1 million participants enrolled by 2019. In addition, the project has convened a PMI cohort Program Advisory Council and conducted a recruitment search for a permanent Director. The Coordinating Center will be funded in February 2016 and will include administration, data, and research support cores. Results from the request for information on the most cost-effective ways of doing physical examinations and collecting biospecimens from volunteers in the United States have been received and will help to the shape the core data collection. The data collection cost will weigh heavily in the final budget and newer tools and cost-effective approaches are available, including the Other Transactions Authority (OTA) mechanism used by the Stimulating Peripheral Activity to Relieve Conditions (SPARC) Common Fund program, as well as by the Defense Advanced Research Projects Agency (DARPA). The OTA, which is designed to obtain cutting-edge technology from non-traditional sources to allow for a high degree of flexibility, has been used extensively by other government entities but has had limited use at the NIH. The OTA approach will be considered for direct volunteer pilot projects and communication support. After the pilot phase awards and pilot testing, the findings will transition to the Coordinating Center starting in July 2016. Rigorous first-level reviews for current solicitations are planned for the Council in May and June 2016.

Discussion Highlights

- " The PMI Cohort Program will establish a core infrastructure for performing targeted studies, which may require the use of smaller subsets to engage specific target populations, including early adopters of advanced mobile technology.

- " A high level of privacy and security will be implemented to ensure participant's genomic data is safe, and data structures capable of policing usage will be in place.

- " The first 1–2 years of the project will be targeted to capturing health-related issues in all age groups, including adolescents. Other strategies would be designed to expand to family engagement.

- " The PMI concept has a global presence, and the U.S. PMI Cohort Program Advisory Panel includes international colleagues, who have helped to shape the some of the ideas for the program.

V. ORIP STRATEGIC PLAN PRESENTATION

Dr. Grieder presented the ORIP strategic plan for 2016–2020, which focuses on infrastructure for innovation. She reminded members that ORIP was established in 2011 and oversees the Division of Comparative Medicine (DCM), the Division of Construction and Instruments (DCI), the Office of Science Education (OSE), and a small-business program. A majority of ORIP's FY 2015 portfolio was managed by the DCM (63%), followed by the DCI (28%), OSE (6%), and small business (3%). The DCM funds Centers and resource-related research projects, including primate, mouse, swine, and zebrafish research and resource centers; investigator-initiated program grants (R01, R21 awards); and veterinary scientist training and career development programs. The DCI provides construction awards to modernize animal research facilities and manages Shared Instrument Grant and High-End Instrumentation programs. The OSE funds Science Education Partnership Awards (SEPA), which establish partnerships between scientists and educators, including education resources for pre-kindergarten through grade 12 as well as science center and museum exhibits to increase, the public's health literacy.

The strategic plan process included focus groups with NIH staff in 2014, followed by outreach to and engagement with the extramural community and the public in 2015. The process revealed high-priority areas, which were distilled into three themes, with strategies outlined for each theme. The first theme is to develop models of human diseases by expanding and ensuring access to animal models, developing and enhancing human disease models and research-related programs, improving the reproducibility of research using disease models, and modernizing and improving animal research facilities to enhance animal maintenance and care. Accelerating scientific discovery with state-of-the-art instrumentation will be accomplished by optimizing the instrumentation program management and providing access to the instruments. Finally, strategies to train and diversify the biomedical workforce include training veterinary scientists as translational researchers; supporting workforce diversity through pre-kindergarten to grade 12 STEM education; continuing rigorous evaluation of SEPA grants; and helping teachers, mentors, and parents improve student interest in science.

Speaking from his experience as a Council liaison, Dr. Terry Magnuson, University of North Carolina at Chapel Hill, School of Medicine, elaborated on Dr. Grieder's discussion of the ORIP strategic plan. Dr. Magnuson highlighted the principles of trans-NIH activities, precision and reproducibility, and improving shared resources, all of which informed strategic plan meeting discussions and guided its direction. He shared examples of how ORIP can play an important role in implementing these principles. In terms of precision and reproducibility, technology advancements in gene editing are accelerating mouse phenotype studies, but the findings are not reproducible because the mice are not being put into repositories. Dr. Magnuson stated that ORIP's Division of Comparative Medicine can assist with this challenge. In addition, as technology continues to evolve, regional consolidation is needed to share costly instrumentation that supports animal systems as resource centers and ensures that trained personnel are available to support technology use. Similarly, the NIH, not ORIP, can help address the problem of supporting critical databases of phenotypes and genomic information that span the NIH. ORIP's Office of Science Education can assist with developing education strategies, such as possible D.V.M./Ph.D. programs, and continuing to promote science tracks starting in the K–12 grades. Dr. Magnuson also lauded the role of ORIP in managing such programs as the shared instrumentation grants program, which allows principal investigators to use high-throughput sequencing technologies in precision medicine studies.

Discussion Highlights

- Š Members recommended that the final strategic plan highlight trans-ORIP interactions that show the Office's integrated activities.

- NIH policy requires investigators to make their models public, but they are not required to deposit them into a repository. Outreach to the scientific community about the need to improve reproducibility may be an effective approach and help to disseminate knowledge about the various mouse models available.

- Members lauded the inclusion of atypical or orphan models and encouraged ORIP to consider trans-NIH animal models of comorbidities.

- Collaboration with organizations that support mentorship, such as the National Research Mentoring Network, may be helpful in diversifying the biomedical workforce, which requires a systems approach with multilevel interactions. Members supported the inclusion of dentistry and veterinary science in the trans-NIH collaboration pool.

- The Big Data to Knowledge (BD2K) Common Fund program is tasked with making databases more interoperable, addressing such topics as storage issues and financial models. Members highlighted several needed resources, such standard-setting vocabularies and access to unpublished work that is not publicly available.

- ORIP advertises the Shared Instrument Grants and High-End Instrumentation Grants programs broadly to the Cancer Centers and other organizations through meetings, discussions, and website updates. These programs do not allow matching-funds activity, but are structured with cost-effectiveness in mind; instrument operators are provided through maintenance contracts.

VI. 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 605 ORIP applications with requested first-year direct costs of $338,639,664. The Council also concurred with the review of 25 responsive Precision Medicine Initiatives applications with total requested costs of $275,698,145.

VII. COMMON FUND CONCEPTS

Dr. Elizabeth Wilder, Director, OSC, provided an overview of the Common Fund strategic planning process, which occurs in two phases. Phase 1 identifies broad scientific areas that the Common Fund could have an investment in over a 5- to 10-year period that would have an impact to the larger NIH community. Ideas for FY 2018 were submitted by external members of the scientific community during an OSC-sponsored workshop. The IC Directors provided additional ideas to identify the biggest challenges in biomedical research and the opportunities with the greatest impact. A subgroup of IC Directors prioritized the compendium of 51 ideas and the top five ideas were presented to the full

[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.

complement of IC Directors. Three ideas generated broad enthusiasm, were recommended for further planning, and are presented as concepts below.

Dr. Wilder reminded the Council that the Common Fund criteria require funded projects to be transformative, catalytic, synergistic, cross-cutting, and unique. Concept clearance is an indication that the idea has been approved for Phase 2 of the strategic planning process. A Trans-NIH working group will be developed for each cleared concept to conduct an NIH-wide portfolio analysis of research on the topic. The working group will conduct workshops, obtain additional input from experts in the area of the concept idea, refine ideas, establish boundaries, and define the focus. The Council will have further opportunities to provide recommendations at the May 2016 meeting. The NIH Director will provide final approval in September 2016.

Discussion Highlights

- Clearance will be by consensus and will occur once in the strategic planning process. If there is not a general consensus, a vote will be taken.

- In the discussion of specific concepts, Council members will decide on the general idea, evaluate the idea against the Common Fund criteria, and provide recommendations. Refined concepts will be provided for additional considerations at the May 2016 meeting.

The following concepts were considered for FY 2018 programs.

Mechanisms of Fatigue in Health and Disease

Dr. Vicky Whittemore, Program Director, National Institute of Neurological Disorders and Stroke, discussed a concept to assess the mechanisms of fatigue in health and disease. Fatigue is defined as the difficulty in initiating or sustaining voluntary activities. One model of fatigue is that work output is a function of motivational input (reward) and feedback from the autonomous nervous system, which establishes the level of perceived exertion. The sense of fatigue occurs when the value of the feedback is much greater than the motivational input or reward; it is poorly understood where or how this calculation occurs.

Fatigue is a major burden for the population in both illness and sleep deprivation; the means for assessing fatigue, however, have not been standardized. Literature reviews identify inconsistencies in measures for assessing fatigue and fatigability across disease entities and across populations. To better understand and to compare fatigability across the different disease entities, the concept calls for the use of the fatigue measures developed by the NIH Patient Reported Outcomes Measurement Information System (PROMIS) to provide assessment standards.

Fatigue is prominent in many disorders and spans across all of NIH. Although the magnitude of fatigue is significant in many illnesses and diseases, the mechanisms associated with fatigue are not well understood. Cancer-related fatigue studies from research led at the NIH by Dr. Leorey Saligan at the National Institute of Nursing Research showed that individuals treated for cancer exhibited acute fatigue symptoms, although not all subjects experienced chronic fatigue. In addition, the biomarker relationship to fatigue was not always correlative, but investigators are continuing to discover promising genomic and mitochondrial biomarkers for cancer-related fatigue. Furthermore, understanding the reward system in the brain will be important for understanding the neural mechanisms of fatigue.

Dr. Whittemore described components of the proposed Common Fund program. The initial phase will begin with pilot "fatigue signature" grants to identify early-stage (responding) biomarkers of underlying

fatiguing conditions in individual cohorts and across different cohorts. After the pilot grants, efforts will move to mechanistic studies to better understand the mechanisms of fatigue. The final phase will include target identifications for interventions at multiple levels, which will eventually lead to pilot treatment trials.

A Common Fund program on the mechanism of fatigue in health and disease is deemed essential because fatigue affects everyone and many individuals across various diseases. Gaps in the knowledge suggest that fatigue is a physiological state that is not well understood and ongoing mechanistic research is limited. This concept proposes a solution to engage the diverse expertise and multidisciplinary approaches that cross multiple ICs at NIH. The goals of the program are to identify mechanisms in physical and mental fatigue and to identify factors that will identify the most vulnerable population(s). Establishing common measures and biomarkers of fatigue would enable future IC-supported projects and inform phase 2 trials of science-based interventions. Identifying peripheral and or central targets that modulate the physiological state of fatigue would enable testing of science-based interventions, and interventions that attenuate fatigue would benefit patients with a wide variety of disorders.

Discussion Highlights

- Data from chronic fatigue syndrome (CFS) studies have not been overly informative about the mechanisms of fatigue, and criteria and measures of fatigue have not been standardized across studies. This project can be relevant for CFS and help establish a systematic approach to understanding common biological relationships relevant to fatigue.

- The goal of the pilot is to identify universal signatures of fatigue, which could identify common processes with distinct mechanisms and elucidate many disease-related behaviors.

- Other strategies to consider are the threshold effect, the aging population, metrics, heterogeneity, fatigue-related side effects from medications, and mouse models of fatigue.

- Fatigue is manifested in disease disorders and sleep deprivation. The effect of sleep on alleviating fatigue will be factored into the concept.

- The initial pilots to ascertain biomarkers will build on previous findings to distinguish between genomic signatures in disease-related fatigue in different cohorts. A significant factor in a decision to close the program would be a failure to identify distinguishing biomarkers.

- Members commented on the very broad scope of the concept and recommended that a balance of biomarker and mechanistic studies be considered. Another strategy might be to use a reductionist approach, in which the concept lies in the purview of individual ICs.

- Phase 2 of the planning process will yield well-defined, short-term goals.

Vote

General consensus was not evident. A motion to clear the concept was forwarded and seconded. The motion passed (15 votes for, 4 against, 1 abstention), and the concept was cleared.

Transformative Potential of High Resolution Cryo-Electron Microscopy

Dr. Jon Lorsch, Director, NIGMS, described the transformative potential of high-resolution cryo-electron microscopy (cryo-EM) as an essential component of the Nation's scientific and technological infrastructure and crucial for positioning the United States in the forefront of cutting-edge biomedical

research. New technological breakthroughs and major advances, such as improvements in signal detection and motion correction, have moved cryo-EM into the atomic resolution domain similar to X-ray crystallography. Scientific opportunities through cryo-EM relate to its ability to determine structures more rapidly and the direct visualization of subcellular structures *in situ.*

The effect of cryo-EM on research spans across all of the NIH ICs and encompasses a wide spectrum of diseases, allowing visualization of structures that are difficult to crystalize and complex molecules, such as ion channels and receptors. It would be instrumental in elucidating the conformational changes in complexes, the effects of mutations on structure, and structures in their physiological environment, as well as in identifying the structural basis of drug action. Cryo-EM has been crucial to recent advances in medicine, including contributing to the development of a possible HIV vaccine.

Dr. Lorsch emphasized that the United States is lagging behind other countries in its access to cryo-EM technology, noting that Europe and Asia have made major investments in high-throughput and regional facilities, whereas the United States is solely invested in a small number of shared facilities. Challenges in the areas of infrastructure, investigator base, and equipment have impeded the advancement of cryo-EM for U.S. researchers. Specifically, the technology is available to only a few experts, a great deal of training and experience is required to operate the instrumentation correctly, and the equipment is very expensive, in terms of both initial purchase and maintenance. The limited use and advancement of high resolution cryo-EM capabilities in the United States stunts the country's growth in research and in technology development.

Dr. Lorsch highlighted a short-term strategy implemented by the NIGMS to support regional consortia with equipment upgrades for existing expert laboratories as a means to improve the current capabilities. The long-term strategy for the Common Fund program is to apply the synchrotron model to cryo-EM technology. The model system would include state-of-the art regional user facilities, with open access to all experienced users selected by a peer-reviewed process, training for users, and technical assistance. In the early stages, the centers would house wet laboratory facilities and offer lodging. Ultimately, establishing the high-throughput and mail-in services models will be major achievements.

The Common Fund concept presented to the Council is to move the United States to the forefront of cryo-EM research by providing efficient and economical access to cryo-EM technologies and training through the creation of regional shared facilities. The project will allow the development of new technologies and computational methods to lower cost, improve resolution, increase throughput and ease of use and push the frontiers of *in situ* cryo-EM.

The proposed budget includes the cost to establish and maintain three regional comprehensive centers, which includes equipment, operations, and training, with an aggregate budget totaling $106.5 million over a 5-year period. This also includes an investigator-initiated technology development effort to focus on cryo-electron tomography, an area of potentially major impact. The implementation would be through the R21 and R01 mechanisms, with estimated costs of $37.5 million over 5 years. The Common Fund would contribute to the cryo-EM program's development over an initial 5 years. Depending on future needs and technological developments, the program could enhance or expand the number of regional facilities in a second phase of Common Fund support. Support for regional facility operations and maintenance is expected to shift over time from the Common Fund to ICs, other federal agencies (e.g., the National Science Foundation, Department of Energy, and Department of Defense), other funders (e.g., the Howard Hughes Medical Institute), and industry.

Following discussion, the concept received positive consensus from the Council.

Discussion Highlights

- Computational training and technical assistance in solving structures for the end user should be included into the portfolio as needed, as well as online training.

- More strategies and incentives should be developed to stem the continuous loss of cryo-EM expertise to other countries. Other strategies could include involving the large NIH workforce of structural biologists who use nuclear magnetic resonance and X-ray crystallography or developing a sabbatical program to encourage skills development.

- Scientific findings from developing cryo-EM are stunning and would have effects across all of NIH. For example, large proteins and their complexes and interactions, which have posed problems for X-ray crystallography, can be addressed with this technology.

- A careful review of other centers to glean their efforts and capacities is an important step toward understanding how the regional centers should be organized. Three centers may not be sufficient to meet the demands for this technology.

- Technology development will be a major effort and should include data analysis and computational support efforts. Other strategies might be to stimulate equipment production in the United States and to engage the small business sector.

- The establishment of regional centers could be approached from two levels: leveraging investments in current centers to expand them to future centers and developing new regional centers. Management of large centers will require a balance of experts from the current centers to facilitate and oversee operations.

The Human Cell Atlas

Dr. Wilder discussed the human cell atlas concept that resulted from Phase I planning. The concept comprises several related ideas from various ICs and can be envisioned as a map of individual cells of the human body and a catalog of all the cell types in the human body. The general ideas revolve around analysis of individual cells and include single-cell analysis to define populations within a tissue, *in situ* analysis to distinguish functions of cells that otherwise appear similar, analyses to define intercellular interactions within a given tissue, genomic analyses to define somatic mosaicism and its impact on cellular function, and technology development.

A major theme in biomedical research is that single-cell sequencing-based technologies have the potential to revolutionize whole-organism science and influence how we understand tissue function. Many single-cell technologies have progressed within the past 5 years, thanks in part to Common Fund investments. Technological advances have led to the identification of new cell populations that are capable of inferring new information on functional responses in various disease states. A Common Fund human cell atlas program would use the single-cell technology to gain a better understanding of organs, their function(s), and how they change during disease.

The goals for a human cell atlas program would be to establish a catalog of human cell types, which would include transcriptional profiling of tissues, characterizations of somatic mosaicism, and the creation of a reference set from comparative studies. The proposed budget would be scalable in anticipation that the atlas would grow over time. Data coordination and technology development will be budgeted for and will leverage current resources at the ICs. The human cell atlas has the potential to be a paradigm-shifting program and would enable research to understand how cell populations change over the lifespan and the definition of cellular impact of exposures to toxic insults. It could also lead to new

parameters in cellular health and disease and elucidate specific drug targets. The atlas would promote new hypotheses, with data mining for continued analysis of investigator-initiated research. The development of new technologies would be broadly enabling at all levels.

Following discussion, the concept received positive consensus from the Council.

Discussion Highlights

- This concept is a hybrid of ideas from several ICs: National Institute of Arthritis and Musculoskeletal and Skin Diseases has proposed an application to understand the difference in inflammation between healthy and disease tissue; NHLBI presented a concept to better understand small blood vessels differences in tissue; and the NCI submitted ideas for new technology and somatic mosaicism. Input from the broader community will shape and prioritize ideas.

- The scope is broad and needs to be refined. One strategy would be to initially develop a reference set of the major cell types and after some time, extend the project to functional assays and imaging.

- This concept will leverage existing technology from single-cell programs in the Common Fund to generate a unique atlas that would be broadly useful to the NIH community.

- The intent of the concept should be clearly defined as a dynamic catalog with cell populations, states, and functions changing over time.

VIII. TRIBAL HEALTH RESEARCH OFFICE

Dr. Anderson described the context and purview of the newly established DPCPSI Tribal Health Research Office. In 2000, the President committed to establishing a process for formal interactions between the tribal nations and all government agencies, so that tribal nations would know what policies were being developed that might affect them and they could have input into what the agencies did and how the policies were developed. In 2009, President Obama confirmed this commitment, and processes are being established, including a trans-NIH advisory committee with tribal representatives, which will meet at least twice each year. The first meeting of the NIH Tribal Consultation Advisory Committee occurred in September 2015.

IX. CLOSING REMARKS

Dr. Anderson returned briefly to the topic of OTA (Other Transactions Authority), noting that it affords nimbleness to an agency in restructuring applications to adapt to changes that may occur during project implementation. DPCPSI is interested in using this funding mechanism in the Common Fund's SPARC program and it could be very useful for the PMI program, as well. He acknowledged that the Council members may not be familiar with OTA and suggested that it be a subject of discussion at a later meeting.

Dr. Anderson thanked the Council members and speakers for their contributions at this meeting.

X. ADJOURNMENT

Dr. Anderson adjourned the meeting at 3:45 p.m. on January 29, 2016.

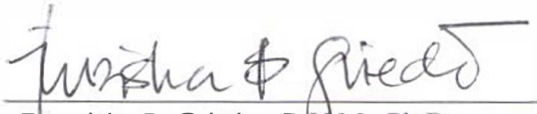
XI. CERTIFICATION

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

3-7-2016

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

Date



3.7.2016

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

Date