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 30, 2015

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 30, 2015, in Building 31, Conference Room 10, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson noted that Drs. Carlos D. Bustamante, Barbara J. Guthrie, and Norbert J. Pelc were unable to attend the day's meeting. Dr. Judy E. Garber participated via teleconference for part of the meeting. Dr. Anderson welcomed eight new Council members. The meeting attendees are identified below.

Dr. Anderson asked Dr. Paul M. Coates, Director of the Office of Dietary Supplements (ODS), Office of Disease Prevention (ODP), DPCPSI, to report on ODS' strategic planning exercise. Dr. Coates said that a progress report for the period 2010 through 2014 is available on the DPCPSI website. He encouraged Council members to review the document and stated that the comment review period will end in early March 2015. A full report on the strategic planning efforts will be provided at the June meeting.

Dr. Anderson reminded attendees that the meeting was mostly open to the public and being videocast. Following introductions and announcements from Franziska B. Grieder, D.V.M., Ph.D., Executive Secretary for the NIH Council of Councils, Dr. Anderson reviewed the day's agenda.

A. Attendance

1. Council Members

Council Members Present

Chair: James M. Anderson, M.D., Ph.D., Director, DPCPSI, OD, NIH
Executive Secretary: Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI, OD, NIH
Philip O. Alderson, M.D., Saint Louis University, St. Louis, MO
Sharon Anderson, M.D.*, Oregon Health & Science University (OHSU), Portland, OR
Marlene Belfort, Ph.D., University of Albany, Albany, NY
Emery N. Brown, M.D., Ph.D., Massachusetts Institute of Technology, Harvard Medical School, Massachusetts General Hospital, Cambridge, MA
Mary Lindsey Carnes, M.D., M.S.*, University of Wisconsin-Madison
Janice E. Clements, Ph.D., The Johns Hopkins University School of Medicine, Baltimore, MD
Ana M. Cuervo, M.D., Ph.D., Albert Einstein College of Medicine, Bronx, NY
Steven T. DeKosky, M.D., University of Virginia, Charlottesville, VA

**Ad hoc member*

Judy E. Garber, M.D., M.P.H., Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
Lila M. Gierasch, Ph.D., University of Massachusetts, Amherst, MA
Susan F. Goekler, Ph.D., M.C.H.E.S., Directors of Health Promotion and Education, Washington, DC
Nancy L. Haigwood, Ph.D., Oregon Health & Science University (OHSU), Beaverton, OR
Hakon Heimer, M.S.*, Schizophrenia Research Forum, Brain and Behavior Research Foundation, 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., Wallace H. Coulter Center for Translational Research, 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 (UNC) at Chapel Hill School of Medicine, Chapel Hill, NC
Craig J. McClain, M.D., University of Louisville School of Medicine, Louisville, KY
Keith A. Reimann, D.V.M.*, University of Massachusetts Medical School, Boston, MA
James E. Schwob, M.D., Ph.D., Tufts University School of Medicine, Boston, MA
Gilbert C. White, II, M.D., Blood Research Institute, Blood Center of Wisconsin, Milwaukee, WI

Council Members Absent

Carlos D. Bustamante, Ph.D., Stanford University School of Medicine, Stanford, CA
Barbara J. Guthrie, R.N., Ph.D., F.A.A.N., Northeastern University, Boston, MA
Norbert J. Pelc, Sc.D., Stanford University, Stanford, CA

2. Liaisons

Jody Engel, Director of Communications, Office of Disease Prevention (ODP), DPCPSI, representing the ODP
Paolo Miotti, M.D., Medical Officer, Office of AIDS Research, DPCPSI, representing the OAR
William Riley, Ph.D., Acting Director of the Office of Behavioral and Social Sciences Research, DPCPSI
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

John D. Harding, Ph.D., Program Director, Division of Comparative Medicine, ORIP, DPCPSI
Louis J. Picker, M.D., Professor of Pathology, Molecular Microbiology and Immunology, and Associate Director, Vaccine and Gene Therapy Institute, Oregon Health & Science University (OHSU)
John Satterlee, Ph.D., Health Scientist Administrator, Genetics and Molecular Neurobiology Research Branch (GMNRB), National Institute on Drug Abuse (NIDA), NIH

**Ad Hoc member*

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH
Elizabeth L. Wilder, Ph.D., Director, OSC, DPCPSI

5. NIH Staff and Guests

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

B. Meeting Procedures

Dr. Grieder reviewed the following:

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

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

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

- Approved minutes will be posted on the DPCPSI website. Minutes from the September 5, 2014, meeting are available on the website.

C. Future Meeting Dates

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

II. DPCPSI UPDATE

Dr. Anderson stated that DPCPSI has prepared a new document, called the *DPCPSI Director's Report to the Council of Councils*, which provides select information from DPCPSI Offices deemed useful for the Council. The document highlights important reports, provides links to high-impact research publications that have been published by DPCPSI staff or DPCPSI grantees, and describes funding opportunity announcements. This new approach is intended to keep the Council informed about the activities of DPCPSI's nine offices, and the Council received the first issue in their electronic materials. He invited comments on the new approach to keeping the Council informed.

Dr. Anderson expressed appreciation to several members for their efforts. Dr. Emery N. Brown, Massachusetts Institute of Technology, is serving on the multi-Council Working Group for the Big Data to Knowledge (BD2K) project, which aims to make NIH-supported data discoverable, accessible, and citable. Dr. Terry Magnuson, UNC Chapel Hill School of Medicine, and Dr. Keith A. Reimann, University of Massachusetts Medical School, are assisting with ORIP Strategic Planning. In addition, Dr. Magnuson will participate as a panelist in a March 28 workshop on Enhancing Efficiency of Research Core Facilities at the Annual Meeting of the Association for Biomedical Research Facilities. The panel

will consider the most efficient use of research facilities supported by the NIH and issues related to centralized management of cores.

Discussion Highlights

- Members agreed that the new *DPCPSI Director's Report to the Council of Councils* is and will be helpful and particularly appreciated the broad perspective provided on the Division's activities and the links to publications and other information.

- Members expressed interest in a report on the BD2K project from Dr. Phil Bourne, Associate Director for Data Science, Office of the Director, at an upcoming Council meeting. Dr. Anderson indicated that Dr. Bourne will be invited to speak at the September 2015 Council meeting.

Inclusion of Women and Minorities in Clinical Research: 2015 Biennial Council Report

Dr. Anderson provided the 2015 Biennial Advisory Council Report on the Inclusion of Women and Minorities in Clinical Research. The NIH Revitalization Act of 1993 requires the NIH Director to ensure women and minorities are included in clinical research and stipulates that each advisory council prepare a biennial report describing how the Institute or Center (IC) complied with the Act.

Dr. Anderson stated that in Fiscal Years 2013 and 2014, ORIP did not support any NIH-defined clinical trials. ORIP projects that included human subjects were exempt from tracking. He provided examples of these projects: Science Education Partnership Award (SEPA) grants were given the exemption "Not to Be Tracked"; and Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants were given the exemption "Not Clinical Research" or "Early Stage of Technology Development." Reviewers in the initial review group are assigned to projects to provide the gender, minority, and children inclusion codes. Inclusion information is provided in the summary statement. ORIP program staff are responsible for ensuring that applicants respond to any concerns regarding inclusion to the satisfaction of ORIP staff and the ORIP Director prior to grant award. ORIP staff regularly attends training activities, including updates on policies and procedures regarding human subjects.

Vote

A motion to approve the 2015 Biennial Advisory Council Report on the Inclusion of Women and Minorities in Clinical Research was forwarded and seconded. The motion passed unanimously.

III. NON-HUMAN PRIMATE (NHP) MODELS

A. NHP Models

Dr. John D. Harding, Program Director, Division of Comparative Medicine (DCM), ORIP, DPCPSI, described NHP model resources funded by ORIP. He stated that the goals of the resources are to provide infrastructure, animals, and expertise for researchers using NHPs; collaborate with grantees funded by any of the NIH ICs and other sources; and provide a central base for researchers performing cutting-edge science using NHPs. Each facility is a national resource. The resources include seven National Primate Research Centers (NPRCs, P51), which are comprehensive, large Centers and in aggregate received approximately $73 million in funding in fiscal year (FY) 2014. Six specialized Centers (P40) are national centers and focus on one predominant NHP species; in aggregate, they received approximately $7 million in funding in FY 2014. A third type of program involves specific pathogen-free macaque colonies, which

are used specifically for HIV/AIDS research and located at the NPRCs and the Caribbean Primate Research Center, with aggregate funding totaling approximately $14 million in FY 2014.

Dr. Harding said that NPRCs house approximately 26,000 NHPs, which include rhesus macaques (60%), baboons, other macaques, and New World monkeys such as marmosets. Approximately three hundred core scientists are resident at the NPRCs snf 2,000 affiliate scientists funded by many NIH ICs make use of the resources and services of the NPRCs. The NPRCs support about 1,000 individual projects annually, with nearly all scientific disciplines involved. Approximately 30 percent of projects focus on HIV/AIDS, including the pathology of viral infection, therapeutics, microbicides, and vaccines.

Discussion Highlights

- The seven NPRCs are linked together as a consortium. There is an Intranet site for internal communication and activity coordination among the Centers, and a publically available online resource (www.NPRCResearch.org) to share information about the capabilities of the NPRCs with the extramural research community and the public (e.g., disease categories, technical capabilities and white papers about the use of NHPs in HIV/AIDS, Ebola, and other disciplines.

- The Primate Centers have coalesced their animal record systems from seven software systems into two systems that cross-talk.

- Council members were encouraged to disseminate information about primate research. Resources and primate models, including phenotype characterization and genetic information, are available on the website www.NPRCResearch.org.

- Training is an important component of the NPRCs, which train investigators, veterinarians, svisiting scientists and students. An opportunity exists to attract and train minority scientists in NHP models. DPCPSI has provided minority supplements to Primate Centers and supports specific training programs through the R25 mechanism.

- Projects funded by Non-NIH entities such as the Department of Defense are performed at the NPRCs.

B. New Science, New Vaccines…Only in the NHP Model

Dr. Louis Picker, Professor in the Departments of Pathology and Molecular Microbiology and Immunology, Associate Director of the Vaccine and Gene Therapy Institute at OHSU, and Senior Scientist at the Oregon NPRC, described discoveries made by researchers at the Oregon NPRC.

Dr. Picker described the utility of applying the NHP model to learn more about human infectious disease and test vaccine efficacy. Captive-bred, Old World monkeys, including the Rhesus macaque (RM), Pigtail macaque, Cynomolgus macaque, and African green monkey, are more closely representative of human infectious disease than any other model. The resemblance with humans can be seen, for example, by the ability to study CD8+ T cells using the same antibodies in RM and humans. Dr. Max Theiler noticed in 1937 while developing the yellow fever vaccine that the yellow fever virus produces nearly identical pathology in monkeys and humans, and simian immunodeficiency virus (SIV) infection of RM results in an immune deficiency syndrome that is similar to that of human AIDS.

Indeed, the RM/SIV model recapitulates many of the pathophysiologic and immunobiologic features of HIV infection in humans. These include the pattern of viral dynamics, mutational escape from immune

responses, patterns of CD4+ T cell depletion, selective loss of effector memory cells, initial stabilization or regeneration of CD4+ memory populations followed by progressive homeostatic failure, persistent and generalized immune activation due in part to microbial translocation, and efficacy of vaccines.

Research conducted during the past 15 years at the Oregon NPRC illustrates the importance of the RM/SIV model in addressing critical infectious disease health threats, including HIV, tuberculosis (TB), malaria, and emerging infectious agents. The RM/SIV model has advanced basic and developmental research and helps explain the failures of HIV vaccine development in the past 30 years. HIV and its counterpart, SIV, are both evolutionarily designed to evade and exploit conventional adaptive immune mechanisms—both cellular and humoral responses. Thus, traditional vaccine approaches have proven ineffective. Studies using the RM model showed a peak immune response approximately 2 weeks after an infection ensued; however, the virus had multiplied to such elevated levels that by the time the immune response peaked, it was too late to control the virus. HIV is adaptive; if the virus grows to a high-replicating titer, the immune response will destroy susceptible viruses, but mutant viruses will emerge and the infection will remain unabated.

In 2000, Dr. Picker began exploring unconventional immune responses that would circumvent the immune evasion mechanism of HIV, particularly the kinetic mismatch between viral replication dynamics and the development of the antiviral effector responses. The cytomegalovirus (CMV) is a persistent virus that remains at a low level in the host but fosters high-frequency effector and tissue-resident memory T cell responses. CMV replicates without causing disease in the 5 or 6 billion people who are infected with it, and evades immune responses sufficiently so that the virus is never cleared. Research showed that 10 to 20 percent of memory T cells are specific for the virus. Although CMV is species specific, the viruses that infect RM are very similar biologically to the viruses that infect humans and were considered as a possible vector for harnessing cell-mediated immunity.

In vivo studies over the years explored whether the immunobiology of CMV could be captured in an effective vaccine vector and found that the virus can elicit and maintain high-frequency effector memory T cell responses in mucosal sites, efficiently super-infect and persist despite robust anti-CMV immunity, and maintain immunogenicity with attenuation. Another finding was that the CMV tegument protein pp71 counters DAXX, a host intrinsic immune protein that blocks the gene expression required for viral replication. pp71 deletion promotes viral latency and results in growth reduction, a lack of vector shedding in secretions, and no vector transmission with co-housing or transfusion. The development of CMV vectors originated from the hypothesis that the effector memory advantage could intercept the infection prior to the upswing in viral replication. Studies of the highly pathogenic SIVmac239 model used intra-rectal, intra-vaginal, and IV routes to determine that CMV/SIV-protected monkeys cleared their controlled SIV infection over time and remained SIV negative for more than 70 weeks. Protection was not affected by preexisting vector immunity, and the majority of protected animals could completely control re-challenge after clearance of initial infection. More than one-half of the overall efficacy may be attributable to differences of SIV-specific T cell responses in all sites of early viral replication, host genetic polymorphisms, or stochastic battle outcome. Additional NHP work will study the clearance of an established SIV reservoir after therapeutic vaccination of SIV-infected monkeys receiving anti-retroviral therapy.

The CMV vector is a platform technology that applies to other vaccine-resistant diseases. For example, TB is highly pathogenic in RM. Monkeys infected with 25 bacilli of *Mycobacterium tuberculosis* died within approximately 4 months; this timeframe provides a clear endpoint for vaccine development. An assessment of rhesus CMV/TB vector efficacy for TB found that although responses for the BCG vector vaccine were different in character from those elicited by RM CMV vectors, they had the same effector memory characteristics. In addition, exposure to the RM CMV vector alone showed a dramatic outcome

in terms of prevention of disease spread in the lung, and especially outside the lung, whereas the combination of BCG and CMV did not work as well.

NHP models have enabled paradigm-breaking discoveries elusive to mouse models or human clinical studies. Analysis of CMV vector immunogenicity showed that SIV-specific CD8+ T cells elicited by CMV/SIV vectors did not recognize conventional epitopes. Advantages of these unconventional responses include potential consistent epitope targeting in all or most vaccines, tolerance of mismatch between vaccine insert and field strain sequences, and use in settings involving escape variants.

CMV is programmable with respect to the epitope recognition of CD8+ T cell responses that they elicit. Research showed that the unconventional CD8+ T cell targeting was associated with the loss of two genes, *UL128* and *UL130*; repair of these genes results in a return to conventional responses. The mechanisms responsible for this epitope switch are under intense study, and correlate with the ability of the CMV vector to replicate in fibroblasts or non-fibroblasts.

These findings in NHP are promising for translation to vaccine research in humans, and a Phase I clinical trial with prototype HCMV/HIV vectors is being planned. Dr. Picker noted that the amount of investment in the development and use of NHP models of infectious diseases has been a key limitation in the ability of the biomedical research community to address the HIV/AIDS epidemic and other infectious disease threats to public health.

Discussion Highlights

- The NHP Consortium, funded by the National Institute of Allergy and Infectious Diseases (NIAID), is examining the onset of protection, with results indicating a consistent infection spread to draining lymph nodes, liver, spleen, and bone marrow. A fully developed reservoir builds quickly within 3 to 4 days in unvaccinated animals, and a combination approach involving latency inducers may be the most effective approach.

- There is a need to increase support of NHP infrastructure, which currently limits the amount of clinical development and basic science research that can be conducted.

- Institutions own the intellectual property for discoveries, which provides an impetus to translate research into treatment for human patients. The NIH's return on investment is improved human health.

- Better protection is provided in the intra-vaginal challenge (24 hours for infection spread) than the intra-rectal challenge (4 hours), likely attributable to greater tissue barriers.

- Initial Phase I trials likely will recruit HCMV-positive men and use peripheral blood specimens, not tissue-resident effector memory cells. Eligibility criteria will be based on the person's own internal response to CMV. Trials to target reproductive-aged women may occur once safety is confirmed.

IV. REVIEW AND VOTE ON COMMON FUND REVISIONS TO THE COUNCIL OPERATING PROCEDURES

Dr. Wilder reviewed revisions to the Common Fund component of the Council Operating Procedures. She noted that the Procedures typically are reviewed annually at the September Council meeting. Discussion

of the Common Fund concept-clearing procedures was deferred in September 2014, however, pending a review of the recommendations from the Common Fund Evaluation. Additional changes were suggested to ensure a more consistent review of applications received through the High Risk/High Reward program. The revisions include the following:

- Conducting the second-level review of the Pioneer and New Innovator awards. The Council provides a second-level review for the Transformative Research and Early Independence awards. The Pioneer and New Innovator awards previously had been reviewed by the Advisory Committee to the Director.

- Engaging IC Directors in the process of vetting concepts prior to the Council's review to allow IC champions to be identified and more well-developed concepts to be considered by the Council. Council clearance would be by consensus; if consensus is not apparent, a simple majority vote by show of hands would determine clearance.

Discussion Highlights

- Vetting process to select concepts for by the Council The vetting process to select concepts for clearance by the Council will be open to any IC Directors who would like to participate.

- The new vetting process will ensure that the Council considers only those concepts that have high enthusiasm from IC Directors.

Vote

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

V. NIH UPDATE

Dr. Lawrence A. Tabak, Principal Deputy Director, NIH, provided a report on NIH activities of interest to the Council, including an update on the NIH's support for biomedical research, the biomedical research workforce, and exceptional opportunities for health science research and discovery. Dr. Tabak said that the NIH's program-level support for biomedical research in terms of constant dollars saw an increase of the budget starting in FY 1998 through 2003 and has become mostly stagnant since 2003. When indexed to FY 1998 dollars, however, funding has been reduced to approximately 2001 levels. A recent article on medical research funding describes the significance of the shifting "ecosystem" of biomedical research funding (*JAMA* 2015;313(2):174–89). The United States' compounded annual growth in research funding has notably leveled since FY 2004, at a time when research opportunities have never been more exciting and more extraordinary. Even so, the Nation remains at the forefront of global medical research, with China and other Asiatic countries following and increasing their investments in biomedical research as seen in terms of their overall gross domestic products. For example, China has increased its number of life science patent applications and medical research articles significantly; China now has a larger science and technology workforce than the United States and is moving ahead in terms of compound annual growth rates. Twenty years ago, biomedical researchers came to the United States for training and generally stayed in the country, contributing significantly to the ability of the Nation to progress. The current situation is that the strongest researchers are either not coming to the United States or not choosing to remain.

Dr. Tabak stated that diversity is essential for the best science, allowing a broadened scope of inquiry, narrowing the health gap, and ensuring fairness, particularly in view of the changing demographics in the United States. If diversity is not achieved, scientific innovation, global competitiveness, training, research on health and equity, recruitment and retention of clinical subjects, and public trust all suffer. Dr. Tabak expressed the NIH's commitment to promoting diversity as a priority across the NIH. A Working Group of the Advisory Committee to the Director (ACD) was charged with reviewing the NIH's efforts in workforce diversity and making substantive and actionable recommendations. The Working Group recognized that the workforce "pipeline" actually functions as a funnel, with underrepresented minorities comprising approximately one-third of college-aged youth but only 6 percent faculty, and recommended the NIH Transformative Diversity Initiative. The Initiative aims to enhance the diversity of the NIH-funded workforce through the Building Infrastructure Leading to Diversity (BUILD) program, the National Research Mentoring Network, and a Coordination and Evaluation Center; awards for these programs, including 10 BUILD sites, were made in October 2014. In addition, in response to the Working Group's recommendation, the NIH Director sought the leadership of an active biomedical researcher with a commitment to diversity and strong credibility in the academic community. Dr. Hannah Valantine was recruited as the Chief Officer for Scientific Workforce Diversity to coordinate the intramural diversity programs across the NIH, experimenting with approaches to improve recruitment and retention of a diverse workforce. All of these programs will be subject to rigorous evaluation.

Dr. Tabak described exceptional research opportunities at the NIH. The BRAIN Initiative involves two 5-year segments: (1) the development of new tools, technologies, and approaches to study the brain; and (2) discovery-driven science. Examples of deliverables for the first segment include a census of neuronal and glial cell types in animal models; a map of neural connections to improve speed, resolution, and throughput; improvements in high-density electrical and optical recording technologies; and technologies for perturbing both the electrical and biochemical activities in defined sets of neurons in real time. Examples for the second 5-year period include extension of the cell-type census to humans; integrated systems for combining measurements; greatly improved, minimally invasive technologies; and systematic theories of how information is encoded in the chemical and electrical activity of the brain.

The NIH has provided a longstanding commitment to research on viral hemorrhagic fevers, including Ebola, through a series of studies in their pathogenesis, as well as the development of various antiviral strategies based on a better understanding of the viral-host interactions. Dr. Tabak referred the Council to the September 2014 issue of *Science*, which includes an article describing how genomic surveillance elucidates the origin and transmission of the 2014 Ebola outbreak. Three Ebola vaccines have been developed, with two in Phase I trials and one ready to launch in a Phase II-III trial, and promising therapeutics such as ZMapp are ready for a trial. Many U.S. agencies have collaborated to support the development of Ebola vaccines and treatments, including the Department of Health and Human Services, Department of Defense, and U.S. Aid for International Development.

Discussion Highlights

- SEPA provides an opportunity to enfold students into the biomedical research pipeline at an earlier age and could complement the NIH program to enhance both workforce diversity and the knowledge base of the citizenry.

- Only approximately 500 of the up to 80,000 Ph.D. degrees awarded annually in the United States are to persons from underrepresented groups. Short-, mid-, and long-term strategies are needed to address the issue. Data are needed regarding how better preparation of student populations who enter college with an interest in science, technology, engineering and mathematics (STEM) education helps with retention within these disciplines. Giving students who have an initial focus

on STEM topics the opportunity to interact with research investigators may improve retention rates.

- Diversity programs should consider ways to engage populations of students from around the world. Global health programs at many universities are developing partnerships to support this level of diversity.

- Underrepresented students might be engaged in the biomedical sciences by learning about health disparities by ethnicity. Cultural influences on education decisions, such as becoming a physician versus a biomedical researcher, also should be considered.

- Concern was expressed about the reduction in funds allocated for evaluation activities in the R25 award mechanism.

Precision Medicine Initiative

Dr. Tabak noted that President Barack Obama announced during his State of the Union address that he was launching a new Precision Medicine Initiative. Council members watched President Obama elaborate on the initiative via a live videocast from the White House. Dr. Francis Collins, Director of the NIH, and Dr. Harold Varmus, Director of the National Cancer Institute (NCI), were present as the President outlined plans for the NIH, NCI, and U.S. Food and Drug Administration to work on different facets of the project. The videocast is available online at http://www.whitehouse.gov/photos-and-video/video/2015/01/30/president-obama-speaks-precision-medicine-initiative.

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 204 ORIP applications with requested first-year direct costs of $92,806,046.

VII. REVIEW OF RECOMMENDATIONS AND DECISIONS FOR PLANNING AND MANAGEMENT OF THE COMMON FUND

Dr. Elizabeth L. Wilder, Director, OSC, DPCPSI, stated that the Council of Councils established the Common Fund Evaluation Working Group (CFEWG) in 2013 to evaluate the principles and processes used to manage the Common Fund, review information from funded programs to assess the impact of Common Fund-supported science, and provide recommendations to optimize the success and impact of the Common Fund. The CFEWG was charged with assessing and advising on processes for strategic

[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.

planning and for managing Common Fund programs. The CFEWG submitted a report in June 2014, including 47 recommendations; the Council discussed and concurred with the report at its September 2014 meeting. After the NIH Director accepted and approved the recommendations, OSC developed responses to the recommendations.

Recommendations for strategic planning involved broad stakeholder engagement to gather and shape ideas; clarify criteria for new Common Fund programs, including those that address urgent needs and those that involve allocation of funds to the Intramural Research Program; provide opportunities for richer participation by the IC Directors as concepts are developed and selected; and enhance partnerships between OSC and ICs through improved working relationships. As part of OSC's response, Phase 1 planning is using a variety of approaches to gather input, such as local and regional meetings of external scientists, broad solicitation of input via social media or requests for information (RFIs), and national conferences. In the future, OSC will enhance opportunities for IC Directors to provide input prior to concept clearance, discuss all concepts in person with the Council to allow richer input, and identify skeptics during Phase 2 planning and have conversations about the value of a particular avenue of research. In addition, OSC will clarify criteria for new Common Fund programs by enhancing interactions between OSC and external stakeholders and between OSC and IC staff by increasing staffing to allow greater interaction with internal and external stakeholders. Outreach to the scientific community will be enhanced at national conferences to increase awareness of the Common Fund and to gather *ad hoc* input on challenges and opportunities.

Furthermore, interactions between IC Directors and Common Fund Working Groups will be enhanced for new concepts. Discussions will clarify criteria with teams that are developing the concept and ensure the program proposal is broadly relevant. OSC also will ensure that programs that form in response to urgent needs are held to Common Fund criteria and processes, albeit on a faster timeline, and will reinforce current policy that states that scientific goals determine a Common Fund program. Intramural or extramural funding can contribute to the strategy to achieve the goals; expectations for intramural-only projects will be clarified via a Memoranda of Understanding (MOU) between OSC and the relevant ICs.

OSC discussed the recommendation to provide opportunities for richer participation by IC Directors and the Council in concept development and selection with the IC Directors at the annual NIH Leadership Forum in November 2014. The IC Directors will be invited to participate via small groups at multiple points during the planning process to help shape new programs and provide input during decision-making prior to concept clearance, prior to finalization of the program proposal, and during the presentation of the proposal to the NIH and DPCPSI Directors. All IC Directors will have the opportunity to provide high-level input on new concepts as they are selected for Phase 2 planning and midway through Phase 2 planning. In addition, fewer but more well-developed concepts will be discussed with the Council for concept clearance. All concepts will be discussed in person.

To strengthen the OSC-IC partnership and to improve working relationships, communications, and transparency as concepts are developed, OSC staffing will be enhanced to support increased interaction; OSC will meet in small and large group settings with IC staff to discuss Common Fund criteria, processes, and plans for program management; IC colleagues will be engaged in fluid dialog as concepts are planned and managed; OSC staff time will be devoted to orchestrate portfolio analyses with Working Groups; and orientation and team building activities with Working Group coordinators will be supported.

Recommendations related to program management were to work fluidly with Common Fund Working Groups to develop a common understanding of goals, milestones, and program management plans; communicate in diverse ways to ensure general familiarity with the Common Fund and ensure that grantees, NIH staff, and end users are aware of goals and deliverables; ensure that evaluation plans are

developed early in program lifecycle and that grantees are fully familiar with end goals and plans to assess the program; engage IC Directors throughout the program's lifecycle.

In response to these recommendations, OSC and experienced IC program staff will mentor new Working Groups on best practices described in the Common Fund Handbook and cover expectations for working together. Enhanced staffing will allow OSC and IC program staff to work as partners to develop a program management plan with flexibility to adapt to changing scientific issues. Annual program review and operating budget planning will be an interactive, bidirectional activity, with OSC program leaders and teams working together to develop a strategy. OSC program leaders will work closely with less experienced Common Fund coordinators in the ICs to relay their experiences and knowledge. In addition, MOUs will be developed with intramural-only programs and initiatives.

To communicate in diverse ways to ensure awareness of the Common Fund and to ensure that grantees, NIH staff, and end users are aware of goals and deliverables, OSC will develop and implement an outreach strategy for the Common Fund program, which will include disseminating information at conferences, professional society meetings, or other venues of relevant audiences. OSC will ensure that each program has an outreach plan that will target relevant investigator communities; initiate a seminar series, to coincide with Council meetings, that highlights Common Fund program accomplishments and deliverables; and ensure that IC Directors are briefed on programs prior to decisions to renew support, as well as invited to Common Fund seminar series. Slides and other communications materials will be shared with IC Directors via a SharePoint site. Principal investigators and IC program staff will be able to review descriptions of processes in the Common Fund Handbook.

To ensure that evaluation plans are developed early in the program lifecycle and that grantees are fully familiar with end goals, Phase 2 strategic planning will continue to emphasize goals and milestones. Additional emphasis will be placed on the negotiation of specific goals and milestones for individual awards via the Notice of Grant Award for all cooperative agreements. In addition, kickoff and annual grantees meetings will be standard for Common Fund programs, and OSC and the Working Group will perform a critical assessment of the program's accomplishments and impact at the midpoint of the funding period, with emphasis on the end-user community.

To engage IC Directors throughout a program's lifecycle, OSC's plans to provide opportunities for richer discussion of Common Fund programs by IC Directors during the planning stages for new or continuing programs, substantive discussion of program accomplishments near mid-point and/or closeout of each program or its transition from Common Fund support, and regular updates on ongoing programs via a seminar series.

Discussion Highlights

- Council members lauded the plans to more fully integrate IC Directors in the Common Fund review process, particularly in substantive discussions of programs during the planning stages, as well as of program accomplishments at midpoint and near their ending. Co-Chairs Drs. Kent Lloyd and Janice Clements also were praised for their leadership of the Evaluation Working Group.

- The evaluation process for individual Common Fund programs should be timely, encompass processes and outcomes, and provide information that can be shared across programs. OSC is committed to implementing a useful evaluation plan and plans to share relevant information among internal staff as one venue of effective dissemination.

- Council members expressed interest in receiving updates and links to Common Fund programs in their pre-meeting materials so they can disseminate accurate information about the Common Fund when attending external events. Brief summaries and statements included on DPCPSI's website and Twitter feed might appeal to younger generations.

- The relationship between the President's Precision Medicine Initiative and the Common Fund has not yet been determined.

- The Working Group's report and recommendations, as well as OSC's response and other documents, will be available on the Council's website.

VIII. COMMON FUND PEDIATRIC RESEARCH PROGRAM

Common Fund Pool—Gabriella Miller Kids First Act

Dr. Wilder presented a concept for a Common Fund pediatric research program. The Gabriella Miller Kids First Act was signed into law on April 3, 2014, and named for a 10-year-old girl who, prior to her death from cancer, called on Congress to take action on pediatric research. The Act ended taxpayer contributions to presidential nominating conventions, transferred the money into the 10-Year Pediatric Research Initiative Fund, and authorizes $12.6 million from the Fund each year for pediatric research through the Common Fund. Use of these funds for any purpose other than making grants for pediatric research as described in the Act is prohibited. The FY 2015 funding bill signed on December 16, 2014, appropriated $12.6 million to the Common Fund for pediatric research as authorized by the Act. The implication is that this money will recur each year for 10 years. In addition, research supported with these funds must meet Common Fund criteria.

Dr. Wilder reminded members that Common Fund programs should be transformative, catalytic, synergistic, novel, and require a high level of trans-NIH coordination. Programs are expected to have exceptionally high and broadly applicable impact, with relevance to many diseases and many ICs. They should either create new approaches to research or clinical care or establish new biological paradigms. Common Fund programs must achieve goals and have specific deliverables that can be achieved within 5 to 10 years. In addition, they should add value to the ICs, address complex issues that require trans-NIH teams and perspectives, and provide new solutions to specific challenges.

The planning process for the Gabriella Miller Kids First initiative began with a trans-NIH Working Group that considered the challenges and opportunities for transformative pediatric research. The group identified strategic planning activities that may have occurred via IC activities and, at a meeting on January 6, 2015, coalesced around the need to build the capability to integrate data from multiple IC-funded pediatric cohorts. Specific ideas included support for genotyping and other data acquisition to participating cohorts, establishment of a computational infrastructure and support for a pediatric data resource, and support for demonstration projects that illustrate the utility of this approach. A small group of IC Directors met on January 20 and endorsed this idea while acknowledging that additional input is needed. Next steps include obtaining input from the community on potential areas of emphasis, the use of integrated pediatric data sets, developing relationships with other data resources or pediatric-specific programs, and exploring opportunities for transformative impact in pediatric research. The Council was informed that discussion with NIH leadership will occur in the spring of 2015 to determine how funds in FY 2015 and beyond will be spent.

Discussion Highlights

- Data collection will focus on critical elements, and cost reductions will be sought by leveraging other programs as appropriate. Cell samples were encouraged as a way for investigators to participate in personalized medicine efforts in the pediatric research field.

- The Initiative's funding of $12.6 million represents new monies and would raise the Common Fund budget to approximately $550 million.

- The age range to be covered by the program has been discussed but not defined. Adult outcomes should be tracked as patients move beyond childhood, although this timeframe would be beyond the Common Fund support period.

- The database infrastructure could incorporate data from well-characterized pediatric cohorts, including whole-genome sequencing, genetic, and phenotypic information, to elucidate disease etiology and pharmacogenomics. The identification and articulation of compelling use cases will be integral in designing the data resource.

- Pediatric researchers should be engaged to determine what compelling questions could be answered with the data. The Cancer Genome Atlas (TCGA) serves as a highly successful and transformational model for research using "big data."

- Health and education records would provide valuable data, but privacy issues as overseen by the Health Insurance Portability and Accountability Act (HIPAA) and Family Educational Rights and Privacy Act (FERPA) must be respected.

- The pediatric population allows long-term followup. The National Children's Study (NCS) included goals to examine long-term outcomes, and samples collected during the pilot project should be considered for use in the Kids First Initiative.

- Environmental factors have an important role in childhood diseases.

- The proposed database could serve an important role in aggregating pediatric data resources, particularly for longitudinal data sets and developmental biology issues.

National Children's Study (NCS): Reallocation of FY 2015 Funds

Dr. Tabak provided a proposal to reallocate FY 2015 funds for the NCS. The NCS was launched under the auspice of the Children's Health Act of 2000, which directed the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) to establish a consortium to plan, develop, and implement a prospective cohort study to evaluate the effects of chronic and intermittent exposures on child health and human development; and to investigate basic mechanisms of developmental disorders and environmental factors that influence health and developmental processes. A pilot project called the Vanguard Study was launched in 2009, but the primary study was never initiated. Two reviews by the Institute of Medicine noted NCS' potential but also highlighted conceptual, methodological, and administrative challenges. Persistent concerns led to the study's being put on hold and an evaluation by an ACD Working Group. The Working Group found that although the overall goals of examining how environmental factors influence health and development are meritorious and should be a priority for future scientific support, the NCS, as currently outlined, is not feasible. It recommended that the NIH champion and support new study designs that are informed by advances in technology and basic and

applied research that could make the original and overall goals of the NCS more achievable, feasible, and affordable.

FY 2015 appropriations included $165 million for NCS. The Bill and report language direct the NIH to maintain the mission and goals of the NCS, while providing NIH flexibility on implementation. The goals for the proposed redirection of NCS funds are to remain true to the original intent of the NCS, specifically by addressing questions at the intersection between pediatric health and the environment, and to support a more focused effort that stresses the engagement of underrepresented communities. The proposed redirection of NCS funds supports three initiatives:

- **Initiative 1: Develop tools that would enhance studies of environmental influences of pediatric diseases.** These include a new initiative on biosensor-based integrated health monitoring systems for environmentally and behaviorally related pediatric health problems, such as wearable (including *in utero*) and static sensors to provide data on environmental and behavioral exposure factors. A new Network providing analysis of children's health exposure offers an integrated infrastructure for the standardized characterization of multiple environmental and genetic factors as determinants of pediatric health. In addition, expansion of the Patient-Reported Outcomes Measurement Information System (PROMIS) project to include clinical validation items banks in children would validate PROMIS measures for children (e.g., obesity, asthma, and juvenile arthritis) with inclusion of environmental components.

- **Initiative 2: Study the influence of the environment on *in utero* development, with the goal of identifying the "seeds" of future diseases and conditions.** Activities would involve expanding the Tox21 Developmental Toxicity program to include a comprehensive testing program of the Tox21 10,000-chemical collection on developmental pathways and cellular phenotypes. In addition, the Human Placenta Project would be charged with developing methods to assess environmental influences on human placental function and fetal development in real time.

- **Initiative 3: Expand examination of environmental influences on later child development by leveraging extant programs.** Supplemental support would be provided to existing children's environmental health cohorts to add proteomic, metabolomics, and epigenetic analyses to well-characterized cohorts, as well as to enhance gene-environment (GxE) interaction studies.

<u>Discussion Highlights</u>

- The proposal to reallocate the NCS funds intends to provide a balanced and encompassing approach for pediatric research by emphasizing the development of tools that can be employed in studies with chemical, behavioral, environmental, and other dimensions. A definition of environmental would be helpful to ensure that the focus is not too narrow.

- Emphasis will be on developing tools that allow researchers to move beyond examining static data from one moment in time to studying response and resilience. The utility of the tools and their potential impact will be realized with the opportunity to develop invaluable longitudinal series as the tools are applied to different cohort studies.

- Discussions and tool sharing with the Superfund Projects and other projects that are developing tools are welcome. The National Institute of Environmental Health Sciences (NIEHS) receives Superfund resources, and related efforts by the National Institute of Biomedical Imaging and

Bioengineering (NIBIB) and the National Institute of General Medical Sciences (NIGMS) are underway.

- The funds are FY 2015 resources for unique projects for unique opportunities and must be spent in the current fiscal year. The NIH faced a similarly daunting challenge when funds were allocated through the American Recovery and Reinvestment Act of 2009 (ARRA).

- Council members expressed appreciation for the proposal's approach to leverage, augment, and integrate resources across existing cohorts and programs.

- Model organism research offers one approach for sensor development.

- The proposal differs from the original NCS in that it leverages existing cohorts; the NCS was intended to build a cohort of children prior to or just after birth and follow them longitudinally up to 18 or 21 years of age. The projects are similar in their focus on pediatric health and environment and the ability to measure these environmental exposures in a broad sense.

IX. UPDATE ON PHASE 2 COMMON FUND PLANNING—ENABLING EXPLORATION OF THE EUKARYOTIC EPITRANSCRIPTOME (E4)

Dr. John Satterlee, Health Scientist Administrator, GMNRB, NIDA, provided an update on the activities of the Common Fund Epitranscriptomics Initiative on behalf of the Common Fund Enabling Exploration of the Eukaryotic Epitranscriptome (E4) Work Group. The Work Group's mission is to identify the key scientific issues in the area of epitranscriptomics for potential development into a new Common Fund program. More than 75 percent of the genome is transcribed into RNA, but only 1.5 percent encodes proteins in the form of messenger RNA (mRNA). In addition to mRNA, RNA comes in many other classes, such as micro- and long noncoding RNA, and its many functions include protein translation, chromatin complex recruitment, and gene silencing. A total of 112 RNA modifications have been identified; far less is known about RNA modifications than about DNA and protein modifications. This scientific gap can be addressed through the study of epitranscriptomics.

The important function of RNA modifications is evident in the example of m6A, the fifth base in mRNA. m6A was discovered in 1975, but interest was minimal until the right tools became available for its study. It has a wide tissue distribution; one publication reported more than 7,000 m6A-methylated mRNAs identified through next-generation sequencing methods. m6A is a reversible modification found near stop codons; methyltransferases (writer), demethylases (eraser), and interacting (reader) proteins, some of which are implicated in human disease, have been identified. m6A has a number of functions: It is, for example, involved in the regulation of mRNA stability, circadian clock control, dopaminergic signaling, mouse fertility, and differentiation of embryonic stem cells. Other RNA modifications also have important roles in human physiology, such as m5C's implication in intellectual disability and pseudouridine's link to cancer susceptibility.

What is currently known about the epitranscriptome represents the tip of the iceberg. The E4 Work Group's activities included a portfolio analysis of existing epitranscriptome research projects, identification of scientific gaps and opportunities, release of an RFI (which yielded 37 responses), and development of a "straw man" program. The portfolio analysis identified 70 NIH-funded grants on inosine, which is involved in RNA editing, as well as a lesser number of grants on other modifications. The analysis found that limited tool and technology development grants currently are being supported.

The Work Group recommended developing a research program focused on a diversity of modifications (beyond inosine), tool and technology development, and increasing *in vivo* mammalian studies.

The Work Group engaged experts to identify critical gaps and opportunities in epitranscriptomics. Tools that would benefit the field include the following: an antibody or other affinity reagent for a particular RNA modification that would enable researchers to investigate that modification in various ways; development of small molecule modulators that could impact the readers, writers, and erasers for these modifications; and computational tools to identify modifications in various data sets. Experts suggested focusing on technology development for low-abundance detection, single-base resolution, and transcriptome-wide assays of modifications; for the detection of RNA modification effects on RNA structure; and for the imaging and manipulation of RNA modifications. A survey of the RNA modification landscape would involve an inventory of known RNA modifications and their readers, writers, and erasers as well as the discovery of novel RNA modifications and modifying enzymes. Another opportunity is to examine the functions of RNA modifications in relation to biological processes, health, and disease.

Dr. Satterlee described an E4 program to catalyze scientists to explore RNA modifications in health and disease and to better understand the RNA modification landscape. The program's two phases focus on: (1) development of tools and technologies for epitranscriptomics to enable scientists to detect RNA modifications; and (2) identification of novel readers, writers, erasers, and modifications, as well as generation of an epitranscriptome catalog. E4 demonstration projects will determine the function of RNA modifications in particular systems. A proposed data coordination center will serve as a central hub to provide user-friendly information to the scientific community through a website and outreach activities, and an IC-supported SBIR/STTR program could allow greater IC participation and support for a more rapid commercialization process of the tools and technologies developed. The Work Group considered how the E4 program would interact with other Common Fund programs, such as analyses of tissue samples from GTEx or body fluid samples from the extracellular RNA program to look for modifications; activities with the Structural Genomics Consortium and Knockout Mouse Project (KOMP) to develop small molecules and mouse models; or collaboration with international funding agencies. Data integration with other relevant data sets also was deemed an important component of the program.

Discussion Highlights

- Members appreciated that the modifications are recognizable chemical entities in a chemical space and can be bound by a small molecule. Spatial data on the 4D nucleome will be integrated when they are available.

- The SBIR initiative provides a venue to accelerate discovery, distribution, and commercialization of significant new tools and reagents. The STTR initiative facilitates partnerships between academia and industry.

- Collaborations with other organizations such as the National Science Foundation are welcome.

X. CLOSING REMARKS

Dr. Anderson thanked the Council members and speakers for their contributions at this meeting. He said that the Core Efficiency Workshop would be held on March 28 in St. Louis, MO. He reminded the members that the next Council meeting will be held on June 19, 2015.

XI. ADJOURNMENT

Dr. Anderson adjourned the meeting at 4:00 p.m. on January 30, 2015.

XII. CERTIFICATION

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

3-2-2015

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

Date

2/27/2015

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

Date