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
May 26, 2017

Meeting Minutes

I. CALL TO ORDER AND INTRODUCTIONS

James M. Anderson, M.D., Ph.D., Director, DPCPSI, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. The meeting began at 8:15 a.m. on Friday, May 26, 2017, in Building 31, Conference Room 10, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson welcomed members and noted that Drs. Melissa Brown, Patricia Hurn, Vivian Lee, and Nsedu Obot Witherspoon were unable to attend and Mr. Jorge Contreras and Drs. Molly Carnes, Sachin Kheterpal, and Keith Reimann were attending by phone. The meeting attendees are identified below. Dr. Anderson also announced new positions for Dr. Sharon Anderson and Dr. Charles Mouton and that Dr. Christine Hunter would be joining DPCPSI as the new deputy director of the Office of Behavioral and Social Sciences Research (OBSSR).

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
Executive Secretary: Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI
Maria L. Acebal, J.D., Food Allergy Research & Education, Inc., Washington, DC
Sharon Anderson, M.D., Oregon Health & Science University, Portland, OR
Cynthia Barnes-Boyd, Ph.D., R.N., FAAN, University of Illinois Hospital and Health Science System, Chicago, IL
Eric Boerwinkle, Ph.D., The University of Texas Health Science Center at Houston, Houston, TX
Molly Carnes, M.D., M.S., University of Wisconsin–Madison, Madison, WI
Jorge L. Contreras, J.D., The University of Utah, Salt Lake City, UT
Jonathan Epstein, M.D., Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
Hakon Heimer, M.S., Schizophrenia Research Forum, Providence, RI
Terry L. Jernigan, Ph.D., University of California, San Diego, La Jolla, CA
R. Paul Johnson, M.D., Emory University School of Medicine, Atlanta, GA
Sachin Kheterpal, M.D., M.B.A., University of Michigan Medical School, Ann Arbor, MI
Kimberly K. Leslie, M.D., University of Iowa Hospitals and Clinics, Iowa City, IA

Jian-Dong Li, M.D., Ph.D., Georgia State University, Atlanta, GA
Guillermina Lozano, Ph.D., The University of Texas MD Anderson Cancer Center, Houston, TX
Terry Magnuson, Ph.D., The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC
Edith P. Mitchell, M.D., FACP, Thomas Jefferson University, Philadelphia, PA
Charles P. Mouton, M.D., M.S., The University of Texas Medical Branch, Galveston, TX
John Postlethwait, Ph.D., University of Oregon, Eugene, OR
Keith A. Reimann, D.V.M., University of Massachusetts Medical School, Boston, MA
Scout, Ph.D., The Torvus Group, Beverly Hills, CA
J. Leslie Winston, Ph.D., D.D.S., Procter & Gamble Global Oral Care, Mason, OH
Gail Yokote, M.S., University of California, Davis, Davis, CA

Council Members Absent

Melissa Brown, M.D., M.N., M.B.A., Thomas Jefferson University, Philadelphia, PA
Patricia D. Hurn, Ph.D., R.N., University of Michigan, Ann Arbor, MI
Vivian S. Lee, M.D., Ph.D., M.B.A., The University of Utah, Salt Lake City, UT
Nsedu Obot Witherspoon, M.P.H., Children's Environmental Health Network, Washington, DC

2. Liaisons

Rachel Ballard, representing **David M. Murray, Ph.D.,** Director, Office of Disease Prevention, DPCPSI
Paul M. Coates, Ph.D., Director, Office of Dietary Supplements, DPCPSI
Karen Parker, Ph.D., M.S.W., Director, Sexual and Gender Minority Research Office, DPCPSI
Janine Clayton, M.D., Director, Office of Research on Women's Health, DPCPSI
Maureen M. Goodenow, Ph.D., Director, Office of AIDS Research, DPCPSI
Wendy Smith, representing **William Riley, Ph.D.,** Director, Office of Behavioral and Social Sciences Research, DPCPSI
Elizabeth L. Wilder, Ph.D., Director, Office of Strategic Coordination (OSC), DPCPSI

3. *Ex Officio* Members Absent

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

4. Presenters

Vivien Bonazzi, Ph.D., Senior Advisor for Data Science, OSC, DPCPSI
Alison Gammie, Ph.D., Director of Training, Workforce Development, and Diversity, National Institute of General Medical Sciences (NIGMS), NIH
Richard J. Hodes, M.D., Ph.D., Director, National Institute on Aging (NIA), NIH
Colin Fletcher, Ph.D., Program Director, Knockout Mouse Phenotyping Program (KOMP2), National Human Genome Research Institute (NHGRI), NIH
Michael S. Lauer, M.D., NIH Deputy Director for Extramural Research
K.C. Kent Lloyd, D.V.M., Ph.D., Professor and Director, Mouse Biology Program, School of Medicine, University of California, Davis
Richard Nakamura, Ph.D., Director, Center for Scientific Review (CSR), NIH
Neil K. Shapiro, J.D., M.B.A., Associate Director for Budget, 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. Announcements and Updates

Dr. Grieder reviewed the following:

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

- Each Council member submitted a financial disclosure form and conflict-of-interest statement in compliance with Federal requirements for membership on advisory councils. The financial disclosures are used to assess real and perceived conflicts of interest, and Council members must recuse themselves from the meeting during discussions of any items for which conflicts were identified.

- Time is 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 April 7, 2017.

- Minutes from the January 27, 2017 meeting are published on the DPCPSI website. The minutes from this meeting also will be published there.

C. Future Meeting Dates

The next Council meeting will be held on September 1, 2017. Council meetings in 2018 will be held on January 25 and 26, May 17 and 18, and September 6 and 7; these dates are reserved, but the duration of each meeting is not yet defined.

II. HISTORY OF THE KNOCKOUT MOUSE PROGRAM (KOMP)

Colin Fletcher, Ph.D., Program Director of the Knockout Mouse Production and Phenotyping (KOMP2) project at the NHGRI, reviewed the history of KOMP. The original idea for the program, published in 2004, outlined a program founded on the completely sequenced mouse genome and supporting a library of mouse embryonic stem (ES) cells and targeted knockouts; live mice would be binned into separate physiological domains, based on preliminary phenotypes, for follow-up with specialized phenotyping. This plan became obsolete when ES cell technology was abandoned in favor of clustered regularly interspaced short palindromic repeat (CRISPR) technology, and discoveries about pleiotropy in mutation effects changed the idea that each knockout is associated with a single phenotype.

Under the original system, knockout mice that did not display the desired phenotype were inaccessible to other researchers, causing waste and extending the time needed to perform comprehensive phenotyping on each knockout strain. Dr. Fletcher pointed out that because NIH funding applications must include preliminary data and a compelling hypothesis, under-studied genes and proteins do not have associated data to gain funding for studies; KOMP supports studies of these genes, providing preliminary data by revealing phenotypes. Thus, a centralized resource allows researchers to access unannotated genes and less-studied proteins, which have continued to languish. Early studies indicate that these under-studied parts of the genome are phenotypically rich and merit further study. Dr. Fletcher commented on a study in

which half the knockout strains displayed between two and five phenotypes, further emphasizing the importance of increasing the understanding of pleiotropy.

KOMP also can assist in setting reproducibility standards. Surveys indicated that about half of all targeted genes in one analysis were retargeted, suggesting that knockouts were not shared. KOMP has shipped many knockouts of unique genes to researchers, and this resource has contributed to more than 1,200 publications, with relative citation ratios between 2 and 19. Guidelines for reporting *in vivo* animal research have been incorporated into the KOMP database, and KOMP has an ongoing effort to study cohorts of both sexes for each knockout, which has led to discoveries of mutations that are expressed differently in males and females.

Dr. Fletcher emphasized that the comprehensive, high-throughput, centralized nature of KOMP is what is necessary to create the level of scale and standardization that leads to discoveries in the areas discussed. Studies of the less-understood sections of the mouse genome already have provided insights in unexpected fields, and further exploration could lead to discoveries of great significance for human health.

III. KOMP2: A TRANSLATIONAL SCIENTIFIC RESOURCE TO CATALYZE BIOMEDICAL RESEARCH AND ACCELERATE PRECISION MEDICINE

K.C. Kent Lloyd, D.V.M., Ph.D., Professor and Director of the Mouse Biology Program at the University of California, Davis School of Medicine, explained that KOMP fulfills the mission of Common Fund programs by translating a scientific resource to catalyze biomedical research and accelerate precision medicine. Each of the three members of the consortium involved in KOMP2 has production and phenotyping components, and the data generated are uploaded to the Data Coordination Center, which serves as the point of association between KOMP2 and the International Mouse Phenotyping Consortium (IMPC). The data are made available on the IMPC website, which also offers primary investigators the ability to register interest in genes, order mice, and engage centers in research.

Dr. Lloyd reviewed the status of the KOMP2 in 2014, when it last was presented to the Council, and described the increases in the numbers of mouse lines produced and phenotyped, phenotypic annotations, orders fulfilled for the research community, and publications. KOMP2 has fully adopted CRISPR/Cas9 technology, and a late adult-onset phenotyping pipeline has been added. The data generated and interpreted by projects within the IMPC have improved the understanding of abnormal phenotypes and identification of homozygous strains that die during development or soon after birth, and the addition of imaging technologies helps determine when these defects appear.

KOMP2 is a 10-year program in its sixth year. Phase 1 fulfilled its goals for production of knockouts and followed thorough reproducibility procedures; Phase 2 aims to produce additional knockout lines and analyze 15 percent of its lines in the late adult stage to look for potential aging phenotypes. Phase 2 also will begin to identify clinical relationships between phenotypes and human disease processes. Dr. Lloyd outlined the process by which data flow from the production and phenotyping centers to the Data Coordination Center, where quality control and association studies are conducted before the data are released to the IMPC portal and the research community.

Dr. Lloyd explained that the ES cell library used in Phase 1 covered nearly the entire genome and included the *lacZ* marker; the CRISPR process used for Phase 2 is more efficient but loses *lacZ*, so technology development will aim to include that marker in the future. CRISPR reduces the number of injections per gene and generates a significantly better germline transmission rate than ES cells. Dr. Lloyd commended the global project centers for rapidly adopting this improved technology.

Dr. Lloyd noted that although creating indels and exdels is straightforward and successful, KOMP2 aims to continue developing more complex alleles; technology to make conditionals is not yet as efficient as desired, and the ability to introduce reporters into alleles also is under study. Although these questions remain unanswered, the time and experience required to conduct KOMP2's research is decreasing because of the use of electroporation rather than microinjection, increasing efficiency for future studies.

The new late-adult pipeline allows researchers to look for phenotypes that may be missed when mice are studied at an earlier adult stage of life. Further, because one-third of genes were confirmed in Phase1 to be essential for life, the embryo lethal and neonatal subviable pipeline will be continued in Phase2. Additional sexually dimorphic phenotypes also have been identified. The broad focus of KOMP2 allows researchers to confirm pleiotropy across genes and phenotypes and to prioritize enrollment of genes with no available knockout or functional annotations. KOMP2 is attributing function for traits, abnormal phenotypes, and potential diseases to these poorly annotated genes, and this attribution will be critical in identifying potential disease-causing genetic variants in human populations. The process begins with analyzing phenotypic similarities between human Mendelian disease and mouse phenotypic associations, then integrate those findings with KOMP-generated data to reveal mouse models, candidates for novel associations, and suggestions for secondary projects. Dr. Lloyd displayed a number of examples of disease models and newly revealed associations across diverse biological systems, noting that the many new discoveries reflect KOMP2's focus on poorly annotated genes.

Dr. Lloyd commented on efforts to integrate KOMP2 with the Mutant Mouse Resource and Research Center (MMRRC), which would utilize the visibility of the MMRRC to enhance the availability and accessibility of KOMP2 lines and data. KOMP2 also is responding to the research community by studying genes that researchers request. Additionally, the functional annotation of genes from KOMP2 can be combined with a clinical precision medicine examination to prioritize variants of unknown clinical significance and create precision animal models that express the specific variants seen in the human population. Dr. Lloyd reviewed the many ways KOMP2 is contributing to research knowledge and engaging with the community and reiterated KOMP2's principles of increasing availability, efficiency, rigor and reproducibility, and preservation of the resource.

Discussion Highlights

- In response to a question about off-target effects, Dr. Lloyd explained that KOMP2 researchers found none in the process of piloting CRISPR/Cas9 technology, and back-crosses to create the cohorts would eliminate any effects that existed. He added that the ability of KOMP studies to inform the use of CRISPR as a clinical technology in humans remains unknown.

- Commenting on the lack of whole-genome sequencing or studies of point or missense mutations, Dr. Lloyd emphasized that KOMP2 must have sufficient resources to complete its mandate to address the protein-coding genome prior to studying additional elements of the genome.

- KOMP2 has not yet studied how phenotypes change in either other inbred mouse strains or in mouse strains that are not homozygous at every allele, but Dr. Lloyd provided an example of a mutation in the C57BL/6N strain used that led to early identification of a phenotype.

- Dr. Lloyd explained that the 15 percent of mice included in the late-onset phenotype pipeline are selected by determining genes that may have a later-onset phenotype but have not yet been described. He acknowledged that this approach is not ideally comprehensive, but it makes the best use of available resources.

- Council members commented on the speed with which CRISPR can respond to new data and asked whether researchers prefer to make their own CRISPR mice rather than utilize the KOMP2 resource. Although CRISPR seems simple, Dr. Lloyd theorized that most of the community understands that the process is complex. Council members recommended gathering data on this question and ensuring that genetic references are available when comparing data from different laboratories.

IV. THE GRANT SUPPORT INDEX (GSI)

Michael S. Lauer, M.D., NIH Deputy Director for Extramural Research, commented that the NIH is entrusted with maximizing the impact of its research dollars and simultaneously ensuring a robust future for the biomedical research workforce. Despite stagnation of the NIH budget since 2003, the capacity of the workforce has increased, creating an unsustainable state of "hypercompetition" that discourages students from entering the profession. The number of scientists applying for funding has doubled since 2003, and the number funded increased only slightly and did so mostly via R21 grants, which are small. Dr. Lauer noted that the number of scientists on the basic R01 grants actually decreased during that time. Evidence suggests that the scientific workforce is aging disproportionately to the general workforce and the distribution of funds is skewed toward a small number of scientists.

These issues prompt consideration of whether resources are being allocated in the most productive way. The GSI plots a measurement of each researcher's support against his or her productivity, showing that although productivity increases as support increases, the rate of increase decreases with increased support. Dr. Lauer commented that because a majority of investigators funded by the NIH have one R01 or less, at any given time these investigators are no more than a few years away from losing all funding and dropping out of the system.

Other studies of the hypercompetitive state of research within the past 15 to 20 years find similar decreases in incremental returns among different groups of researchers. Dr. Lauer suggested that in this environment, the funding portfolio could be made more productive by funding more scientists; the number of researchers at work is a greater determinant of scientific production than the amount of money invested. He added that, because scientific discovery involves some degree of serendipity, funding the work of as many researchers as possible increases the likelihood that some will make major discoveries. The challenge is to give researchers enough money to conduct legitimate research and simultaneously fund as many researchers as possible.

The relationship between productivity and laboratory size also has been studied, finding that larger groups are more productive, but a pattern of diminishing returns means the increase in productivity is less notable as more researchers are added. Dr. Lauer also discussed a study that found no association between mentor funding and production of Early Stage Investigators.

A workshop to diagnose issues in biomedical research identified two core problems—too many researchers are vying for too few dollars, and too many postdoctoral researchers are vying for too few faculty positions—and designated any other issues, such as the stress placed on the peer review process, as symptoms of these core problems. Strategies to address these problems include redistributing funds to support junior investigators and pioneering projects or capping the funding available to a single laboratory or single principle investigator.

The 21st Century Cures Act includes a provision requiring the director of the NIH to develop policies that promote new researchers and earlier research independence. Dr. Lauer noted that existing strategies addressing this question have halted the decrease in new investigators, but numbers have not begun to increase. This provision could be fulfilled by equalizing the success rate of early stage and established

investigators, increasing the funding for early stage investigators, providing a 1-year award to applicants who fall slightly short of the payline, or developing additional trans-NIH approaches.

NIH has contemplated the best way to measure any particular investigator's support, measuring support in such a way as to account for the disparity in cost for different kinds of research and avoid penalizing those who work in a field that is inherently more expensive. Therefore, the NIH has suggested a metric called the "Grant Support Index," which is effectively a modified grant count that is benchmarked to a value of 7 points for each R01. NIH is proposing gradually resetting expectations regarding the maximum level of support an individual investigator can receive. The NIH Office of Portfolio Analysis has found that only 3 to 5 percent of investigators received funding above the proposed cap of 21 points or three R01s, which would allow the creation of 900 new awards, and added that the cap would include a trans-NIH exceptions process. He explained that feedback suggested the caps lower the point value from 7 to 5, allowing a single person to have as many as four R01s, which is very rare. Dr. Lauer suggested that special considerations may be needed to attract highly talented investigators into new or niche fields of science. He reiterated NIH's commitment to nurturing the next generation of researchers and optimizing its resources.

Discussion Highlights

- In response to a question about whether financial savings for these projects would affect projects like KOMP, Dr. Lauer acknowledged the challenge of balancing budgets without funding increases but explained that taking funding from programs like KOMP that generate their own efficiency was not an attractive option.

- Council members agreed that new investigators should be supported but expressed concern over the proposed strategies, noting that many of the best investigators meet the cap and are discouraged from seeking additional promising collaborations for fear of exceeding that level. Members questioned the premise on which the cap was based and commented that NIH's focus on reproducibility should extend to data affecting policy.

- In response to a question about grants that specifically help young investigators, Dr. Lauer described the current handicaps provided to Early Stage Investigators and acknowledged that the separation of reviews for young investigators requires further assessment. He pointed out that many investigators are disappearing from the system shortly after their first R01, so retention may depend both on funding Early Stage Investigators through a certain point and providing a handicap to those who have done good work on a single grant.

- Dr. Lauer commented on the clinical research perspective of this issue, noting that competition and the costs of medical school affect recruitment of physician scientists. He added that clinical research is generally more expensive than non-clinical research, so caps that have been requested by the basic science community would severely damage some clinical researchers.

- In response to a question about the decision to centralize the exceptions process, Dr. Lauer commented on the contrast between independent activities of the Institutes and Centers (ICs) and the perception of funders that the NIH is a single entity. Council members noted that ICs will be more knowledgeable than a trans-NIH group about the research conducted in their fields. Dr. Lauer noted that this effort has prompted some IC directors to reexamine whether researchers are not being funded by multiple ICs for the same work.

- Council members asked for clarification regarding how the GSI scores grants with multiple principle investigators or no-cost extensions; Dr. Lauer acknowledged that these issues have not

yet been resolved. Although the caps would not apply to co-investigators, Council members pointed out that the GSI would affect large percentages of investigators at collaborative centers.

- Dr. Lauer hoped that these changes would help in the high-priority effort to diversify the workforce; Council members cautioned against proceeding without putting specific plans in place to ensure increased diversity.

- Dr. Lauer confirmed that there has been consideration of making allowances for investigators participating in service activities or mentoring.

V. PROGRESS AND PLANS AT THE NIA

Richard J. Hodes, M.D., Ph.D., Director of the NIA, explained that the NIA was established in 1974 to conduct research on aging processes and diseases and needs particular to older people. Similar to other ICs, the NIA trains scientists, provides resources, and disseminates the results of research; it also has an intramural research program, which supports the broader research community with such efforts as the Baltimore Longitudinal Study on Aging. This study began in 1958 and is arguably the longest comprehensive longitudinal study of aging. Previous studies of aging typically compared college students to older people in nursing homes, but this longitudinal study illuminated the process of aging in a different way, and it has become a resource for much research.

Within the NIA, the Division of Aging Biology studies the underlying molecular and cellular mechanisms of aging in both human and animal model systems and, therefore, covers a broad range of genetics and physiology. One concept guiding this research is the idea of "geroscience," the convergence of the biology of aging and its underlying processes with the biology of disease. Because aging is a major risk factor for nearly all major chronic diseases, interventions that target the basic biology of aging may affect multiple diseases. Dr. Hodes pointed out that Dr. Francis Collins' work on models of premature aging is an example of the way the study of genetics has contributed to the understanding of both a particular condition and the underlying mechanisms of aging. He explained that established programs within this division test new interventions that could prolong life, proposed by individuals or identified from published work, in a way that ensures their rigor and reproducibility.

The Division of Geriatrics and Clinical Gerontology focuses on both geriatrics as a science and the study of aging in human systems in models. Clinical research in this division includes participation in the National Heart, Lung, and Blood Institute's (NHLBI) Systolic Blood Pressure Intervention Trial. Dr. Hodes noted that the NIA became interested in this study to determine whether the strongly positive results would apply to older adults, but the same results occurred in individuals 75 and older. The NIA often collaborates on other ICs' studies in this way to emphasize aging as a variable.

The largest division within the NIA is the Division of Neuroscience, which recently received significant budget increases targeted to Alzheimer's disease. This division conducts basic neuroscience on the biology of aging in the nervous system, including motor and sensory functions, and also emphasizes cognitive health and dementia. Studies made possible by the recent funding increases have increased the understanding of high-risk genetic determinants of neurological disease and tested ways to identify biomarkers and track disease long before symptoms appear. Dr. Hodes discussed a study of early onset dementia in which clear increases in amyloid load were visible on a PET scan beginning 20 years before expected onset and plateauing before symptoms appear. He noted that until recently, treatment could begin only at the onset of symptoms and thus failed to make an impact, but this new early identification led to clinical trials aimed at preventing progression. Dr. Hodes stressed that research into Alzheimer's disease incorporates many disciplines, so research not explicitly targeting Alzheimer's disease may be important to what neuroscientists hope to accomplish in this area.

The Division of Behavioral and Social Research studies the reversibility of early-life risk factors, regional and international differences in health and longevity, and the social neuroscience of aging. Dr. Hodes commented on the failure of the United States to echo other countries' decreases in mortality of individuals, ages 45 to 54, noting that surveillance at the population level is critical to identifying problems and ways to intervene. This division is supporting clinical trials of behavioral interventions, such as a method to reduce inappropriate prescription of antibiotics using prompts in the electronic health record. Another study supported by this division looked for interventions to improve the health status of both individuals with dementia and their caregivers and, in addition to showing general success, demonstrated that the best interventions were not always the same across racial/ethnic subpopulations. The study is being pilot tested through the Indian Health Service and modified to help caregivers of veterans with traumatic brain injury and spinal cord injuries. Dr. Hodes emphasized that the racial and ethnic differences successfully documented in that study were noticeable because the study was conducted with appropriate attention to those subgroups.

Discussion Highlights

- In response to a question about drug repurposing and long-term side effects, Dr. Hodes noted that metformin is used widely for diabetes but may have effects on multiple diseases. Researchers also have begun to study whether senescent cells could be killed selectively, which could be a complement to drug repurposing.

- Dr. Hodes emphasized the success of public-private partnerships, particularly in Alzheimer's disease research, and described a potential program in which the NIA can fund supplements for researchers whose projects may have Alzheimer's disease implications.

- Dr. Hodes confirmed that dementia interventions being tested on those whose risk is identified early are the same medications that were not successful in treating individuals at later stages. Because amyloid buildup plateaus at later stages, target engagement could not be identified, so trials at early stages may be able to confirm whether these drugs have the intended effect.

- The NIA utilizes both printed materials and substantial online channels to communicate with the general public, and they partner with multilingual organizations. Council members suggested that periodic video highlights of NIA's research could help the Institute publicize its efforts, as the ways people find information about aging continue to evolve.

- Dr. Hodes commented on the potential costs and applicability of screening tests that would allow scientists to move beyond imaging; research on ways to identify biomarkers in spinal fluid, serum, or plasma eventually could translate into broadly available tests.

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

[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.

affirmed by all Council members present. During the closed session, the Council concurred with the review of 85 ORIP applications with requested first-year direct costs of $24,537,681. The Council also concurred with the review of 833 responsive Common Fund applications with first-year direct costs of $1,426,575,994.

VII. A STUDY OF POSSIBLE BIAS CONCERNING RACE, GENDER, SENIORITY AND INSTITUTION, AND WITHIN THE PEER REVIEW PROCESS

Richard Nakamura, Ph.D., Director of the CSR, explained that the CSR reviews 70 to 75 percent of NIH grant applications, ensuring the reviews are fair, independent, expert, and timely. The NIH review process is challenged by record numbers of applications, reviewer burnout, and rigor and reproducibility concerns. CSR is evaluating different approaches to improve the review process. The Center also studies how to appropriately distribute applications across study sections, measure quality across applications, and changes to the application scoring system that might allow reviewers to better convey their assessments.

Dr. Nakamura said that the steadiness of NIH's budget since 2003 shows how its mission is valued, but the buying power of that budget has decreased and the number of applications has increased. This situation has pushed application success rates to historic lows, which can discourage individuals considering a career in science. Dr. Nakamura theorized that this competition was a major cause of the problems around rigor and reproducibility.

He then focused on the confusion that rose after NIH modified it applications to enhance rigor and reproducibility of its research. The application now asks for more attention to be paid to the scientific "premise" of a study to ensure that its scientific foundation is sound, but applicants and reviewers often interpret this as a request to ensure the study has a rational hypothesis.

The CSR also expects reviewers to assess whether applicant plans to address sex as a biological variable are adequate and explain how their resources will be authenticated; single-sex studies and contaminated cell lines have led entire areas of science astray. These new efforts are intended to ensure that studies are judged by the best practices in their fields and provide adequate information about the underlying science. Dr. Nakamura emphasized that exploratory studies still are allowed and the potential for impact remains an important consideration.

To improve review quality, the CSR surveyed reviewers; reviewers were generally very positive about their experiences. In cases of poor reviews, the CSR communicates with the study's program officers and institutional review board to identify the sources of concern. The reviewer surveys also showed that reviewers assessed electronic review meetings less positively than face-to-face meetings. Dr. Nakamura noted that CSR has improved its electronic review platforms.

The CSR is conducting an anonymization study to determine whether bias is related to the lower success rate of African American grant applicants. Dr. Nakamura explained that, though the application does not specify an applicant's race, scientific disciplines are small enough that at least one reviewer frequently is aware of the applicants' race. For this anonymization study, all clues to the applicant's ethnicity, sex, career level, and institution have been removed from previously reviewed applications, and these applications are being reviewed again to determine whether anonymization affects the preliminary scores.

Dr. Nakamura said CSR regularly consults with other scientists to improve peer review; however, any promising ideas proposed would lead to studies rather than immediate changes. One possible strategy is a retrospective review of applicants' publications, which might better illustrate a scientist's rigor than a project-oriented application. Deadlines for submissions could be eliminated to allow scientists more time

to consider whether their application is sound. Applicants could be required to review other applications in the same pool, which would both illuminate any biased self-evaluations and increase the pool of potential reviewers.

Dr. Nakamura noted that the rapid evolution of technology requires the CSR and the NIH to improve constantly. A number of other countries have surpassed the United States in financial commitment to research, and the NIH must consider whether the number of scientists trained should be reduced if they cannot be supported. On a more positive note, the unemployment rate of scientists remains low despite the recession, most scientists consider their jobs to be rewarding and valuable, and Congress recently has shown increased support for biomedical science.

Discussion Highlights

- Dr. Nakamura explained that reviewers in the anonymization study are being asked to comment on the applications' grantsmanship and whether they can identify the anonymized data. Council members recommended asking reviewers to comment on any perceived bias, and Dr. Nakamura requested feedback on language that could be interpreted as biased.

- Council members commented on application scores that converge when discussed within a study section; this tends to increase divergence between scores across multiple study sections.

- In response to a question about project officers' dislike of meetings that are not face-to-face, Dr. Nakamura agreed that experience with virtual meetings increases comfort and noted that the quality of the meetings is affected strongly by the ability of the Chair to maintain engagement.

- When asked whether the increase in team science makes it difficult to find reviewers who can evaluate the full breadth of an application, Dr. Nakamura acknowledged that there is much to learn about how to review multidisciplinary science and noted that applications with a weakness in one discipline often are unsuccessful because of that weakness.

VIII. COMMON FUND DIVERSITY PROGRAM

Elizabeth Wilder, Ph.D., Director of the OSC, commented that the NIH has been trying to increase diversity for many years, but effects were seen only on the individual level. The Common Fund Diversity program is a new and experimental system, so its methods will be evaluated rigorously and the most effective components will be disseminated.

Alison Gammie, Ph.D., Director of Training, Workforce Development, and Diversity at the NIGMS, explained that the Diversity Program Consortium (DPC) is taking a scientific approach to enhancing diversity. It operates simultaneously on the student, faculty, and institutional levels and integrates social science research and psychosocial interventions. The program is in the third year of the first phase, developing and implementing interventions and evaluations as well as publishing early findings. The second phase will continue existing projects and add a focus on the sustainability and dissemination of the interventions.

DPC's partners are the Building Infrastructure Leading to Diversity (BUILD) network, which connects more than 100 diverse institutions across the country, and the National Research Mentoring Network (NRMN), which has participants in all 50 states. Some of DPC's interventions—such as providing financial assistance, research experiences, active learning courses, supportive learning communities, mentor training, and professional networks—are instituted at the consortium-wide level. Interventions at the site-specific level include reducing stereotype threat, imposter syndrome, microaggressions, and

unconscious bias, as well as emphasizing cultural awareness and support systems. Some BUILD sites also include psychosocial interventions, efforts to partner with research-intensive institutions, and innovative efforts to recruit populations of students who might not otherwise consider biomedical research.

Robust evaluation of successes is key to maintaining DPC's scientific approach. The Coordination and Evaluation Center (CEC) has developed both site-specific and consortium-wide evaluation plans in coordination with the sites, and the entire consortium has agreed to CEC's data-sharing agreement. Hallmarks of student success tracked in the evaluation may include engagement in research, publication, or decision to pursue a biomedical career; longer term outcomes include majoring in or receiving a degree in a biomedical field. Dr. Gammie emphasized the long-term nature of this program—there may be 20 years between a student's entry into undergraduate school and biomedical research independence.

Psychosocial metrics that can be tracked include scientific identity or self-efficacy. At the student level, researchers theorize that exposure to BUILD activities will result in a stronger science identity and increased persistence in a biomedical major, graduation with a biomedical bachelor's degree, and matriculation to graduate school in biomedical science; questions that measure science identity have been scattered throughout the evaluations. Dr. Gammie noted that a control group is not possible in this kind of study, but defining a comparison group is important. A faculty-level hypothesis theorizes that interventions contributing to self-efficacy will improve research-related success. The institutional-level study of features that contribute to increased participation in biomedical research can be evaluated using diversity of biomedical majors and graduation rates before and after interventions are established.

Several of DPC's efforts already are demonstrating success. The site-specific and consortium-wide evaluation plans are ready for dissemination, and data suggest the interventions are reaching underrepresented populations. Additionally, the NRMN has grown into a national mentoring hub, institutions are committing to the development of biomedical programs, and research activities at the sites are increasing. As the DPC moves into its second phase, it will continue to gather data on these interventions and translate them into sustainable models for increasing diversity beyond the funding period and disseminating effective strategies to increase biomedical diversity on a national level.

Discussion Highlights

- Council members described effective diversity strategies at their institutions. Dr. Gammie commented on the creativity of many approaches and noted that a gap remains in the diversity of Ph.D. awardees and faculty hires.

- In response to comments emphasizing the negative effects of imposter syndrome on diverse candidates, Dr. Gammie agreed that psychosocial factors must be considered at every career level; mentors from diverse communities may be especially important in overcoming psychosocial challenges.

- When asked how BUILD institutions were selected, Dr. Gammie explained that institutions are limited to domestic baccalaureate-granting colleges/universities that receive less than $7.5 million (total costs) of NIH research project grant (RPG) funding annually and have an award-eligible pool of undergraduate students, at least 25% of whom are supported by Pell grants. These eligibility requirements are intended to target funds to relatively under-resourced institutions with a demonstrated commitment to students from financially disadvantaged backgrounds. Additional institutions may be added in future cycles; this would stimulate new innovations but require significant lead time.

- Council members emphasized the need to collect and prioritize data on sexual and gender diversity, especially given the Council of Councils' advocacy of the Sexual and Gender Minority Research Office.

IX. NIH BUDGET DEVELOPMENTS

Neil K. Shapiro, J.D., M.B.A., Associate Director for Budget, NIH, explained that the 21st Century Cures Act provided funding for four Innovation Projects: the Precision Medicine Initiative Cohort program or *All of Us* Research[SM] program, the Brain Research through Advancing Innovative Neurotechnologies Initiative, the Cancer Moonshot, and a new regenerative medicine project studying clinical research on adult stem cells. These funds will be appropriated each year but are not subject to discretionary spending caps; they vary from year to year because Congress wanted offsets to avoid increasing the deficit, and the availability of offsets changes each year. Mr. Shapiro emphasized that changing levels in the Cures Act do not reflect a change in NIH's intentions for those research programs, and funds from the Cures Act will need to be combined with other annual funds to achieve the total funding sought. The non-defense discretionary cap for fiscal year (FY) 2017 is roughly the same as FY 2016; the cap for FY 2018 is slightly lower under current law.

The recent passage of the 2017 Consolidated Appropriations Act allowed the NIH a funding increase of 6.2 percent, with approximately 3 percent applicable to all ICs, and larger increases for certain projects. This increase occurred late in the fiscal year after several continuing resolutions, which included emergency supplemental appropriations to develop vaccines against the Zika virus. Appropriations from other areas were transferred to the vaccine effort last year, and Mr. Shapiro noted that similar funding of Ebola research in previous years has prepared the NIH well to work on the current Ebola outbreaks in Africa.

Mr. Shapiro explained that the FY 2018 President's Budget is lower than in past years; the Consolidated Appropriations Act, 2017 was not received in time to use as the baseline, so this budget was based on the FY 2017 continuing resolutions. Mr. Shapiro commented on the proposal to merge the Agency for Healthcare Research and Quality with the NIH and dissolve the Fogarty International Center, noting that some of the activities currently conducted by the Fogarty International Center would continue within the Office of the Director. He explained that because the budgeting process occurred later than usual, the Congressional appropriations process likely will be accelerated, and a continuing resolution for FY 2018 at the end of September is likely. Mr. Shapiro hoped that final bills will be enacted within the typical timeframe of December to January but acknowledged that other Congressional activities could delay the appropriations process. He also noted that some Congressional leadership indicated an intention to continue increasing the NIH budget.

<u>Discussion Highlights</u>

- When asked whether funds transferred from Ebola research to Zika research will return to their initial designation, Mr. Shapiro explained that the initial 2-year funding for NIH already has been obligated, but some amounts with longer timeframes were in reserve at the Department. He did not have information on the current funding status but affirmed that Ebola research remains a high priority.

- In response to a question about the NIH policy on the indirect recovery rate, Mr. Shapiro commented on the intent to maintain as much research as possible at the requested funding level. He noted that the NIH spends about 28 percent of the extramural budget on indirect costs, compared to 10 percent payment by foundations. Council members commented on the challenges that budget reductions pose to hiring young investigators and cost-sharing between institutions.

Mr. Shapiro acknowledged that the 2018 budget includes a general provision limiting research grant salaries.

- Mr. Shapiro was asked how critical activities are funded when the budget does not provide adequate funding, and although he is not party to discussions at that level, he theorized that the decreases in non-defense spending were not specifically targeted at the NIH.

X. UPDATE ON PLANS OF THE NIH DATA COMMONS

Dr. Wilder introduced the NIH Data Commons, a trans-NIH initiative that receives funds from the Common Fund and all ICs. Vivien Bonazzi, Ph.D., Senior Advisor for Data Science in the OSC, played a central role in developing the NIH Data Commons, which is piloting systems for making NIH-wide data findable, accessible, interoperable, and reusable—or FAIR. Dr. Bonazzi noted that generating data that do not follow FAIR principles is costly in terms of time, effort, energy, and money. She emphasized that using data at scale must be done cooperatively.

The NIH Data Commons will begin by reviewing three high-value data sets: NHLBI's Trans-Omics for Precision Medicine Project, NHGRI's model organisms databases, and Common Fund's Genotype-Tissue Expression Project. The Data Commons incorporates a sharable, cost-effective computer storage platform—large data sets are stored and used in the cloud, rather than requiring local storage or large downloads. This method requires users to be highly competent in computational biology and cloud systems; Dr. Bonazzi suggested that if data are stored but not used by the wider scientific community due to high barriers to entry, data science at scale has not been achieved.

Unifying principles that allow data to be used after it has been shared must be defined; Dr. Bonazzi emphasized that storage and usage technology should not affect the data. Digital platforms that can perform these functions exist, but biomedical science requires more complex systems. Dr. Bonazzi stressed that the NIH must determine how digital platforms affect the way that science can be conducted.

Pilots underway to study the Commons principles include the National Cancer Institute cloud pilots and the Human Microbiome Project, and the Big Data to Knowledge program intends to provide funds for additional trans-NIH projects. Dr. Bonazzi also highlighted the importance of education to promulgate FAIR data principles within the NIH.

Establishment of metadata standards is critical—data can be found only if the search tools surrounding it are readable by all. Dr. Bonazzi noted that metadata often have been neglected in past NIH studies. Authentication and authorization of those who access the data also is important; because much of the data is from human subjects, data must be safe, secure, and private. Additionally, the NIH must develop relationships with cloud companies that allow work to be conducted between clouds and follow best practices that meet the FAIR guidelines.

Challenges include rapid changes in the field and technology; Dr. Bonazzi noted that any policies developed will quickly become out of date with the technology and vice versa. She emphasized the importance of supporting existing community data standards, rather than driving the effort from the NIH. Cloud companies have certain business models, and the NIH pays for the use of the cloud from grant funding; consideration of how NIH's business model works with others is important.

In terms of implementation, the cloud is pay-as-you-go—an analysis can be done either quickly and expensively or over a longer period of time at a lower cost. The current cloud service marketplace model does not adequately account for all costs or ways the system will be used in the long term, and it does not create a FAIR relationship between the researcher and cloud provider.

Dr. Bonazzi discussed making data from different fields, such as genotype and expression data, interoperable to allow researchers to answer interdisciplinary questions. Ideally, all users would agree to FAIR standards and use them to collaborate; this would create a true commons.

The first step to moving in this direction will be to utilize the three pilot data sets and their existing tools. Applications that can operate over the data sets also may be available. Utilization of workspaces for particular projects or data sets will drive collaboration, because scientists working on the same project will be able to see all analyses in the same place and conduct analyses across data sets. Dr. Bonazzi acknowledged that strategies for enabling work flows have not yet been adequately developed.

Determining the appropriate architecture for data commons projects will require testing and analysis of the complicated financial structure of cloud usage.

Discussion Highlights

- Dr. Bonazzi confirmed that additional NIH data sets would be incorporated, but she did not have an anticipated timeline. She clarified that many commons already exist, and these should be made interoperable, rather than attempting to create a new, monolithic commons. If a set of standards can be agreed upon, innovation will build on that foundation.

- Council members recommended developing ways for data from other agencies to be incorporated into a larger commons, and Dr. Bonazzi confirmed that conversations with data scientists in other organizations already are in progress.

- Regarding Commons storage of negative results, Dr. Bonazzi suggested that all available data should be findable, but acknowledged that it may not be practical to store all data sets on the cloud. It may be sufficient for some data to be accessible within individual communities.

- Council members emphasized the importance of training and outreach to ensure that all members of the general research community can utilize the data.

XI. CLOSING REMARKS

Dr. Anderson thanked the Council members and speakers for their contributions at this meeting. He reminded the members that the next Council meeting will be held on September 1, 2017.

XII. ADJOURNMENT

Dr. Anderson adjourned the meeting at 3:58 p.m. on May 26, 2017.

XIII. CERTIFICATION

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

James M. Anderson -S
Digitally signed by James M. Anderson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=2000562943, cn=James M. Anderson -S
Date: 2017.07.10 16:37:58 -04'00'

07/10/2017

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

Date

Franziska B. Grieder
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DN: cn=Franziska B. Grieder, o=NIH, ou=ORIP, email=griederf@mail.nih.gov, c=US
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07/10/2017

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

Date