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

Council of Councils Meeting
September 8–9, 2022

Meeting Minutes

Day 1

I. CALL TO ORDER AND INTRODUCTIONS

Robert W. Eisinger, Ph.D., Acting Director, DPCPSI, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. Ms. Maria L. Acebal and Drs. Graham A. Colditz and Kevin C. Kent Lloyd were unable to attend. The virtual meeting began at 10:15 a.m. on Thursday, September 8, 2022. The meeting attendees are identified below. Dr. Eisinger then reviewed the day's agenda.

A. Attendance

1. Council Members

Council Members Present

Chair: Robert W. Eisinger, Ph.D., Acting Director, DPCPSI
Executive Secretary: Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI
Maria Rosario G. Araneta, Ph.D., M.P.H., University of California, San Diego, La Jolla, CA
Kristin Ardlie, Ph.D., Broad Institute of Harvard University and Massachusetts Institute of Technology, Cambridge, MA
Linda Chang, M.D., FAAN, FANA, University of Maryland School of Medicine, Baltimore, MD
Andrew P. Feinberg, M.D., M.P.H., Johns Hopkins University School of Medicine, Baltimore, MD
Rick Horwitz, Ph.D., Allen Institute for Cell Science, Seattle, WA
Patricia D. Hurn, Ph.D., R.N., University of Michigan, Ann Arbor, MI
Kevin B. Johnson, M.D., M.S., FAAP, FACMI, FIAHSI, FAMIA, Annenberg School for Communication, University of Pennsylvania, University of Pennsylvania Health System, Philadelphia, PA
R. Paul Johnson, M.D., Emory University School of Medicine, Atlanta, GA
Karen C. Johnston, M.D., M.Sc., University of Virginia, Charlottesville, VA
Paul J. Kenny, Ph.D., Icahn School of Medicine at Mount Sinai, New York, NY
Sachin Kheterpal, M.D., M.B.A., University of Michigan Medical School, Ann Arbor, MI
Gary A. Koretzky, M.D., Ph.D., Weill Cornell Medical College, New York, NY
Richard D. Krugman, M.D., University of Colorado School of Medicine, Aurora, CO
Jian-Dong Li, M.D., Ph.D., Georgia State University, Atlanta, GA
Edith P. Mitchell, M.D., FACP, Thomas Jefferson University, Philadelphia, PA
Charles P. Mouton, M.D., M.S., M.B.A., The University of Texas Medical Branch at Galveston, Galveston, TX

Megan O'Boyle, Phelan-McDermid Syndrome Data Network, Arlington, VA
Rhonda Robinson-Beale, M.D., UnitedHealth Group, Minneapolis, MN
Susan Sanchez, Ph.D., The University of Georgia, Athens, GA
Jean E. Schaffer, M.D., Joslin Diabetes Center, Harvard Medical School, Boston, MA
Scout, Ph.D., National LGBT Cancer Network, Pawtucket, RI
Anna Maria Siega-Riz, Ph.D., M.S., University of Massachusetts Amherst, Amherst, MA
Russell N. Van Gelder, M.D., Ph.D., University of Washington, Seattle, WA

Council Members Absent

Maria L. Acebal, J.D., The Aspen Institute, Washington, DC
Graham A. Colditz, M.D., Dr.P.H., M.P.H., Washington University School of Medicine in St. Louis, St. Louis, MO
Kevin C. Kent Lloyd, D.V.M., Ph.D., University of California, Davis, Davis, CA

2. Liaisons

Joseph M. Betz, Ph.D., Acting Director, Office of Dietary Supplements, DPCPSI
Janine A. Clayton, M.D., Director, Office of Research on Women's Health, DPCPSI
Maureen M. Goodenow, Ph.D., Director, Office of AIDS Research, DPCPSI
Belinda Seto, Ph.D., Deputy Director, Office of Data Science Strategy (for **Susan K. Gregurick, Ph.D.,** Director, Office of Data Science Strategy, DPCPSI)
Franziska B. Grieder, D.V.M., Ph.D., Director, ORIP, DPCPSI
Christine M. Hunter, Ph.D., ABPP, Acting Director, Office of Behavioral and Social Sciences Research (OBSSR), DPCPSI
Christopher J. Lynch, Ph.D., Acting Director, Office of Nutrition Research (ONR), DPCPSI
David M. Murray, Ph.D., Director, Office of Disease Prevention, DPCPSI
Irene Avila, Ph.D., Assistant Director, Sexual & Gender Minority Research Office, DPCPSI (for **Karen L. Parker, Ph.D., M.S.W.,** Director, Sexual & Gender Minority Research Office, DPCPSI)
Rebecca Meseroll, Ph.D., Health Science Policy Analyst, Office of Portfolio Analysis, DPCPSI (for **George M. Santangelo, Ph.D.,** Director, Office of Portfolio Analysis, DPCPSI)
Marina L. Volkov, Ph.D., Director, Office of Evaluation, Performance, and Reporting, DPCPSI
Elizabeth L. Wilder, Ph.D., Director, Office of Strategic Coordination (OSC), DPCPSI
David R. Wilson, Ph.D., Director, Tribal Health Research Office, DPCPSI

3. *Ex Officio* Member Absent

Tara A. Schwetz, Ph.D., Acting Principal Deputy Director, NIH

4. Presenters

Franziska B. Grieder, D.V.M., Ph.D., Director, ORIP, DPCPSI
Richard Hodes, M.D., Director, National Institute on Aging (NIA)
Christine M. Hunter, Ph.D., ABPP, Acting Associate Director for Behavioral and Social Sciences Research (BSSR) and Acting Director, OBSSR, DPCPSI
Chris Kinsinger, Ph.D., Assistant Director for Catalytic Resources, OSC, DPCPSI
William Klein, Ph.D., Associate Director, Behavioral Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute (NCI)
Christopher J. Lynch, Ph.D., Acting Director, ONR, DPCPSI
Oleg Mirochnitchenko, Ph.D., Program Officer, Division of Comparative Medicine (DCM), ORIP, DPCPSI

Stephanie J. Murphy, V.M.D., Ph.D., DACLAM, Director, DCM, ORIP, DPCPSI
Amanda Melillo, Ph.D., Chief, Integrative Biology and Infectious Diseases Branch and Director, Oral Opportunistic Pathogens and Viral Disease Program, National Institute of Dental and Craniofacial Research (NIDCR)
Adam H. Russell, D.Phil., Acting Deputy Director, Advanced Research Projects Agency for Health (ARPA-H)
Sheri Schully, Ph.D., Deputy Chief Medical and Scientific Officer, *All of Us* Research Program
Lawrence A. Tabak, D.D.S., Ph.D., Performing the Duties of the Director, NIH

5. NIH Staff and Guests

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

B. Announcements and Updates

Franziska B. Grieder, D.V.M., Ph.D., the executive secretary for the NIH Council of Councils, 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 August 8, 2022, and revised on August 18, 2022.
- Minutes from the May 19–20, 2022, meeting are posted on the DPCPSI website. The minutes from this meeting also will be posted there.

C. Future Meeting Dates

The next Council meeting is scheduled to be held January 19–20, 2023. Additional future meetings are scheduled May 11–12 and September 7–8, 2023.

II. NIH UPDATE

Lawrence A. Tabak, D.D.S., Ph.D., Performing the Duties of the NIH Director, provided an update on the NIH, beginning with leadership changes. Dr. James Anderson retired as DPCPSI Director, and Dr. Eisinger is Acting Director. Dr. Ned Sharpless has retired as Director of the National Cancer Institute (NCI), and Dr. Monica Bertagnolli will be appointed as the next Director. Dr. Anthony Fauci will retire as Director of the National Institute of Allergy and Infectious Diseases. Dr. Michael Gottesman stepped down as NIH Deputy Director for Intramural Research (DDIR), and Dr. Nina Schor is serving as Acting DDIR. Mr. Kevin Williams has been appointed as the Director of the Office of Equity, Diversity, and Inclusion, and Dr. Adam Russell has been appointed the Acting Deputy Director of ARPA-H. Dr. Tabak pointed out that the NIH budget has increased steadily in recent years, but a continuing resolution is likely before the beginning of this coming fiscal year on October 1. Appropriations for 2022 represented a 5.2

percent increase over 2021, and the general increase for all Institutes and Centers (ICs) was 3.4 percent, with a number of specific increases for various areas.

The COVID-19 pandemic has caused more than 1 million reported deaths in the United States and 6.5 million deaths worldwide; case numbers and virus circulation remain high. At the end of August 2022, the BA.5 variant represented about 90 percent of cases, and each successive variant has been more transmissible. The new bivalent boosters target the BA.4 and BA.5 strains, as well as the ancestral strain. Several varieties of FDA-authorized COVID-19 mRNA vaccines—the first kind of vaccine developed—now are in use; adenovirus vector–based vaccines were the next developed, and the most recent FDA-authorized vaccine is a more traditional subunit protein vaccine.

A global outbreak of monkeypox that began in May has reached about 42,000 confirmed cases. The NIH, in collaboration with its AIDS Clinical Trials Group, has begun a trial of TPOXX for outpatients with monkeypox, which will include people with HIV. Another clinical trial of TPOXX in people with monkeypox has begun in the Democratic Republic of the Congo, in partnership with the United States. An upcoming open-label study of intradermal administration of low-dose JYNNEOS monkeypox vaccine is designed to extend safety and efficacy data sets and inform the ability to stretch the limited quantities of this vaccine currently available.

All Federal agencies, including NIH, are charged by the White House with developing new or updating existing plans by February 2023, to maximize public access to scientific data. Scholarly publications will not be embargoed, scientific data will be made accessible upon publication, and persistent digital identifiers and metadata for all research outputs will be required. Current public access policies scheduled to be implemented within the next several years are being reviewed and revised, an extensive consultation process is in progress, and NIH will continue to collaborate with stakeholders and other agencies as the policies are developed. Dr. Tabak emphasized that this represents a cultural shift, but expressed confidence that the NIH can work with publishers to meet the spirit and intent of this change.

Regarding ongoing COVID-19 initiatives, the Researching COVID to Enhance Recovery (RECOVER) Initiative is working to better understand how to predict, treat, and prevent post-acute sequelae of SARS-CoV-2 infection (PASC or long COVID). RECOVER aims to understand the biological and clinical foundations of COVID-19 recovery as a function of time, define risk factors to understand incidence and prevalence, categorize PASC subphenotypes, and identify treatment interventions. RECOVER is a patient-centric effort on a national scale and aims to be as inclusive and diverse as possible, with substantial community engagement. All platforms are using standardized methodologies and common data elements, and the initiative will adapt based on emerging science. The National COVID Cohort Collaborative (N3C) studies the clinical course of COVID-19 using electronic health record data from more than 15 million people, 6 million of whom had documented COVID-19 cases, in 49 states. The data are computed in a secure environment, but many training and community resources are available. N3C data have been reported in numerous publications and helped define risk factors for Long COVID, confirm monoclonal antibody treatment effectiveness, and assess Paxlovid rebound. A public–private partnership between NIH and a number of other entities, based on Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) initiatives, aims to identify better treatments for severe respiratory infection and maintain the clinical trials infrastructure for pandemic preparedness. Potential therapies include small molecules, such as protease inhibitors; monoclonal antibody use for passive immunity; immunomodulatory agents targeting host pathways; combination therapies; and supportive care approaches.

Discussion Highlights

- Dr. Tabak commented that efforts to identify a new NIH Director are ongoing, but a nominee has not been identified.
- Dr. Tabak clarified that data accessibility will not be the responsibility of journals, but multiple approaches likely will be required. He explained that the current open-access business model for publishers could limit the contributions of early-stage and underrepresented investigators through its high costs, but NIH will explore how to expand its public access model—which requires investigators to deposit a copy of their manuscript in the NIH system before submission to journals—while minimizing unintended consequences. Dr. Tabak agreed that more nuanced methods of assessing researchers' productivity are needed. Council members also suggested that NIH assess how the public access policy would affect leadership of Center or program project grants.
- In response to suggestions for improving the RECOVER initiative, Dr. Tabak clarified that enrollment will increase as participants with active COVID-19, some of whom will develop long COVID, are followed longitudinally.
- Dr. Tabak commented that research undertaken because of innate curiosity sometimes can lead to remarkable, yet unpredictable, discoveries, such as CRISPR-Cas9.

III. ORIP CONCEPT CLEARANCE: REISSUE OF RESOURCE-RELATED RESEARCH PROJECTS FOR DEVELOPMENT OF ANIMAL MODELS AND RELATED MATERIALS (RFA-OD-19-027)

Stephanie Murphy, V.M.D., Ph.D., DACLAM, Director, DCM, ORIP, introduced for concept clearance the reissue of the Resource-Related Research Projects for Development of Animal Models and Related Materials program using the R24 funding mechanism. The objective of this program is to encourage grant applications to develop, characterize, or improve animal models of human diseases; develop or improve technologies and methods that aim to enhance rigor and reproducibility of research with animal models; improve access to information about or generated from the use of animal models of human disease; and improve diagnosis and control of diseases of laboratory animals. The funds available and the anticipated number of awards for this program are contingent upon NIH appropriations and submission of meritorious applications. The award project period is 4 years.

The Animal Models R24 program was established in 2010 by the National Center for Research Resources (NCRR) and has continued to evolve under ORIP administration since 2012. To align with ORIP's mission on awarding grants to support research resources, such as animal models of human diseases, this R24 program meets the demand for animal models that are more predictable and accessible for biomedical research and addresses the need for a broad array of animal models that mimic the pathogenic events leading to various diseases. Under the current funding opportunity announcement (FOA), RFA-OD-19-027, 19 of 81 applications have been funded to date, an award rate of 23 percent. Since 2013, ORIP has issued three FOAs for this R24 program, with 74 of 297 applications funded to date at an overall award rate of 25 percent.

A major theme of the *ORIP Strategic Plan 2021–2025* is facilitating the development and ensuring the availability of the highest quality and most useful animal models and related resources for the advancement of research on human disease. As part of its NIH-wide emphasis, ORIP seeks to improve and disseminate the best animal models that are of interest to multiple ICs. ORIP has sustained an Animal Models R24 program to encourage resource-related research to develop, characterize, or improve animal models of human diseases;;; develop or improve technologies and methods that aim to enhance rigor and

reproducibility of research with animal models; improve access or information about or generated from the use of animal models of human diseases; or improve diagnosis and control of diseases in laboratory animals. Proposed R24 projects must have broad application to multiple NIH ICs and must explore multiple organ systems or evaluate diseases that affect multiple organ systems.

The Animal Models program has continued to make significant progress and impacts under ORIP's administration. The 74 awards made under the three most recent FOAs, from 2013 to the present, have resulted in 915 publications, with approximately 83 percent of these awards having at least one publication since 2014. As of July 2022, these publications have been cited more than 23,000 times. An analysis of the translational impact of these publications using *iCite* shows that publications from these awards cluster primarily between animal-oriented research and molecular/cellular research. Thirty-two percent of these 74 awards focused on model development; 25 percent focused on technology development or information generation; and 14 percent focused on colony management innovations. Most of these awards supported widely used animal models, including rodents, such as mice and rats, in 31 percent of awards; aquatics, such as zebrafish and frogs, in 30 percent of awards; invertebrates, such as fruit flies and nematodes, in 20 percent of awards; and nonhuman primates (NHPs) in 15 percent of awards.

The Animal Models R24 program has generated many new animal model resources and related materials, such as transgenic animals and molecular reagents. For example, an R24 award to Baylor College of Medicine led to the development of more than 6,000 transgenic flies now publicly available through the Bloomington *Drosophila* Stock Center, also supported by ORIP. This R24 program has produced a vast amount of detailed information related to animal models, including atlases and validated information on animal stocks. For example, the Jackson Laboratory used its award to validate Cre-driver mouse strains, and the strain information posted online receives more than 50,000 page views annually. The program has created new and improved technologies, including imaging, genetic engineering, and cryopreservation approaches. An example of this is an award to the Pennsylvania State University Hershey Medical Center that resulted in enhanced microcomputed tomography technology, 3D reference images of zebrafish, and computational tools for high-throughput tissue phenotyping. The resources and information derived from the Animal Models R24 program are widely shared, accessed, and used by the research community, and they have significantly impacted biomedical research.

Discussion Highlights

- The discussants, Drs. Paul Johnson and Susan Sanchez, provided their comments. Both strongly supported the concept, and Dr. Sanchez emphasized the importance of animal models to the biomedical research enterprise.
- In response to Dr. Johnson's questions, Dr. Murphy explained that ORIP has released a separate funding opportunity for model validation. She clarified that the Animal Models R24 Program supports colony management innovations, but not day-to-day operations. She also explained that such tools as web portals and search engine tools are considered informational resources. Model. M organism databases would not be supported by this program.
- Dr. Murphy acknowledged Dr. Johnson's suggestion to review the program's impact more broadly and look for specific grants that may have resulted from the Animal Models R24 programs.
- When asked about research currently excluded from the request for applications (RFA), such as genome sequencing, that would address existing models more fully, Dr. Murphy explained that the notice of intent to reissue this FOA, released in July, includes further details on this initiative. Some other ORIP mechanisms support such research, including the Animal Models R21 Program, but research with a primary focus on genome sequencing would not be a good fit for

ORIP support. Dr. Murphy encouraged potential applicants to discuss their concepts with ORIP prior to applying to ensure the best fit.

Vote

A motion to approve the reissue of the Resource-Related Research Projects for Development of Animal Models and Related Materials concept was forwarded and seconded. The motion passed with one abstention.

IV. INFORMATIONAL CONCEPT UPDATE: NATIONAL INSTITUTE OF FOOD AND AGRICULTURE/U.S. DEPARTMENT OF AGRICULTURE (USDA) AND NIH: DUAL PURPOSE WITH DUAL BENEFIT RESEARCH IN BIOMEDICINE AND AGRICULTURE USING AGRICULTURALLY IMPORTANT LARGE DOMESTIC ANIMAL SPECIES (R01)

Dr. Grieder provided an update on the program entitled, "Dual Purpose with Dual Benefit Research in Biomedicine and Agriculture Using Agriculturally Important Large Domestic Animals". The initiative includes several NIH Institutes, Centers, and Offices (ICOs) and the National Institute of Food and Agriculture (NIFA) at the USDA. This program aims to stimulate and encourage investigations in biomedicine and agriculture through the use of pertinent large domestic farm animals that mimic specific human developmental, physiological, or disease states.

Dr. Grieder explained that recent congressional report language urges the restarting of this interagency program. Historically, large domestic farm animals have contributed to fundamental knowledge regarding the physiology and pathophysiology of organ systems and the development of reproductive technologies. The congressional committee expects NIH to continue this cooperative partnership and strengthen ties between human medicine, veterinary medicine, and animal science, with the goal of improving animal and human health and enhancing applicability and return on investment in research. Dr. Grieder noted that the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and NIFA previously collaborated on funding opportunities that supported research on assisted reproduction technologies, fetal physiology, birth control, neuroendocrinology, muscle biology, diabetes, and obesity.

The program goals are to (1) fund excellent research that addresses problems in both human health and animal agriculture, (2) advocate utility of large domestic farm animals as models to study high-priority areas in both biomedical and agricultural research, (3) encourage scientists working with large domestic farm animals to become part of the NIH research process, and (4) provide training opportunities and incentives for animal and veterinary scientists to apply for NIH grants. Applicants must address at least one priority research area, target a problem important to both human health and animal agriculture, and use large domestic farm animals as experimental models.

Discussion Highlights

- Council members highlighted examples of large domestic farm animal models, including sheep as models for cerebral circulation and pigs as models for stroke and heart disease. They emphasized the need to determine how well the models simulate human disease at the molecular and cellular levels. Dr. Grieder agreed and reiterated that this program focuses on building bridges between proposed models and human disease. Two relevant examples include milk feeding in pigs and hepatitis C in horses. She noted that investigators at veterinary schools often express that the research will benefit both humans and animals.
- Dr. Grieder explained that the plans for ICO partnerships are limited to the current scope of the program, but it could be expanded in the future.

- Dr. Grieder clarified that the program initially was discontinued because of a lack of highly meritorious applications. When asked whether an analysis could be performed as an example of shifting away from the use of NHPs in biomedical research, Dr. Grieder responded that she was unaware of such a study, and large farm animals are used infrequently in biomedical research. This concept could be explored in the future.

V. NEW ORIP CONCEPT CLEARANCE: SOMATIC CELL GENOME EDITING TESTING CENTER

Oleg Mirochnitchenko, Ph.D., Program Officer, DCM, ORIP, presented a new concept clearance entitled, "Testing Centers for Development of Somatic Cell Genome Editing in Model Organisms". The objective of this initiative is to provide broadly applicable resources and testing services in reporter animals and disease models to investigators developing somatic cell genome-editing therapeutics relevant to the interests of multiple NIH ICOs. The initiative would fund three Testing Centers focused on rodents, pigs, and NHPs.

Recent technologies, such as CRISPR-Cas9, have catalyzed the development of experimental genome-editing therapeutics. Numerous genetic diseases potentially could be treated using these new approaches, but further testing and new animal models are needed. Dr. Mirochnitchenko explained that the initiative is aligned with the *ORIP Strategic Plan 2021–2025*. The new Testing Centers will facilitate the development and ensure the availability of the highest quality and most useful animal models and regulated resources for the advancement of research on human disease; improve and disseminate the best models for human conditions and diseases that are of interest to multiple NIH ICs; and advance application of new technologies to support research resources and improve the generation, care, preservation, and distribution of animal models.

The current NIH Common Fund (CF) Somatic Cell Genome Editing (SCGE) program is developing new reporter animals and testing new delivery modalities. The initiative comprises seven grants, all of which are administered through ORIP. The specific focuses of the current SCGE program are to generate reporter animals and to validate and test delivery technologies. Dr. Mirochnitchenko explained that currently, testing is being performed in healthy animals, and the program is focused on development of the delivery technologies. Additionally, he noted that program resources currently are available only to SCGE Consortium investigators. Distribution of reporter animals and new cohorts will require additional coordinated support.

To align with ORIP's NIH-wide mission, the proposed new Testing Centers should (1) have the ability to use wild-type and reporter animals, as well as disease models, relevant to the interest of multiple NIH ICOs; (2) have the capacity and expertise to evaluate genome editing across a variety of disease conditions; (3) offer resources and services to the wider biomedical community that have a significant impact on the rigor and reproducibility of animal studies; (4) provide animal resources and services to assist in the development of new technologies and preclinical testing to generate high-quality, reproducible information required for clinical studies; (5) coordinate their activities with the SCGE program, as well as other programs at NIH ICOs, such as the Bespoke Gene Therapy Consortium and the Ultra-Rare Gene-based Therapy (URGenT) Network; and (6) develop outreach and advertisements for the program to solicit requests for fee-for-service use and collaborative studies.

Dr. Mirochnitchenko noted that the new Testing Centers would perform proof-of-concept studies using prenatal gene editing in large animal species for the treatment of inherited genetic diseases. This need was emphasized at both the SCGE Program Phase 2 Planning Workshop in 2021 and joint UCSF/FDA Prenatal Somatic Cell Gene Therapies Workshop in 2021.

Discussion Highlights

- The discussants, Drs. Kristin Ardlie and Rick Horwitz, provided their comments. Both discussants expressed support for the initiative.
- Dr. Ardlie asked for clarification on the distinction between the current SCGE program and the Testing Centers. Dr. Mirochnitchenko explained that the current program funds four Testing Centers, which develop reporter animals and conduct testing. Support for the Small Animal Testing Centers will expire in mid-2023, and support for the Large Animal Testing Centers will expire in early 2024. He explained that these Testing Centers serve only investigators funded through the program, whereas the new program would support access by the broader biomedical research community.
- Dr. Ardlie also asked about the capacity of each Testing Center to support research projects. Dr. Mirochnitchenko remarked that the current SCGE program can serve as a basis for cost estimation. Generally, small-animal projects require 3 to 4 months, and large-animal projects are likely to require about 1 year. The Small Animal Testing Centers likely could support 10 to 15 projects per year, and Large Animal Testing Centers likely could support 3 to 5 projects per year. A fee-for-service program could help increase available funds and expand the capacity. Dr. Mirochnitchenko added that collaborations with other NIH ICOs would provide additional capacity.
- Dr. Horwitz asked for more information on the source of the disease models, as well as the selection process for disease models. Dr. Mirochnitchenko responded that ORIP supports large Resource Centers that contain a wide collection of well-characterized animal disease models. Additionally, the Resource Centers maintain collections of publications on the use of those specific models for specific applications. This information is stored in databases and made available to the public. These resources could be incorporated into the new program, and joint expertise would be leveraged. Additionally, collaborations would be fostered across the Testing Centers.

Vote

A motion to approve the Testing Centers for Development of Somatic Cell Genome Editing in Model Organisms concept was forwarded and seconded. The motion passed with one abstention.

VI. NEW CF CONCEPT CLEARANCE: HUMAN VIROME PROGRAM

Amanda Melillo, Ph.D., Chief of the Integrative Biology and Infectious Diseases and Director of the Oral Opportunistic Pathogens and Viral Disease Program, NIDCR, introduced for concept clearance the Human Virome Program, a new CF program. The objective of the program is to characterize the human virome and define its role in health and disease. Initiatives in the first phase of the program—which is projected to span 5 years—are to characterize the human virome in longitudinal, diverse cohorts across the life span; develop tools, models, and methods to interrogate and annotate the human virome; elucidate the human host–virome interactome; and support a Data Analysis and Coordinating Center.

The primary focus of the program will be the commensal human virome, which encompasses numerous families of viruses. Dr. Melillo highlighted the example of anelloviruses, a diverse family of viruses; many questions remain regarding the biology of the anelloviruses. Dr. Melillo emphasized that the human virome is large and diverse and has been understudied. The virome's interactions with the human body, and long-term effects on health and disease, are unknown. To date, nearly all studies of the virome have been small scale. Opportunities exist for NIH ICOs to support virome studies that align with their specific

priorities. Dr. Melillo highlighted examples of human virome studies, which include immune responses, cancer, pathogenic infections, substance use disorder, childhood obesity, and celiac disease.

The NIH CF established a trans-NIH working group to address knowledge gaps related to the human virome. The working group is composed of 20 members from 12 ICOs. The working group published a request for information in March, and a virtual workshop was held in April to inform the development of this program. The members also performed a portfolio analysis across NIH and other funding agencies; they found that funding for research on the fundamental understanding of the human virome was limited. The goal of the workshop was to gather information on the current state and knowledge of the human virome to identify critical gaps, which included virome diversity and dynamics; timing and mechanisms of establishment; definition of a healthy virome; virome–host immune system interactions; functional and multiomic studies; definition of the exposome; and technical innovations for isolation, quantification, and propagation. Other needs include animal models, standardized protocols, a reference sequence database, and annotation and contamination detection tools.

Dr. Melillo highlighted potential deliverables of interest, which include novel contributors to health and disease, novel insights into the development of the immune system and responses to vaccines, novel biomarkers for disease or therapeutic efficacy, novel viral vectors for gene therapy, a human virome reference sequence database and bioinformatic innovation, and robust data sharing and standardization. She asserted that this program supports the overall NIH mission and fits the criteria for CF programs. Additionally, she highlighted synergistic opportunities, which include leveraging other NIH efforts, as well as partnerships with the National Science Foundation, U.S. Department of Energy, Global Virome Project, International Committee on Taxonomy of Viruses, American Type Culture Collection, and U.S. Department of Agriculture Animal and Plant Health Inspection Service.

For initiative 1, the program will solicit applications to characterize the human virome in longitudinal diverse cohorts that cover the life span. For initiative 2, the program will solicit applications to develop tools, models, and methods to integrate and annotate the human virome. Initiative 3 will solicit applications to elucidate the human virome–host interactome, including identifying the relevant exposome that modulates the virome and defining interactions within the immune system and discovering host cells that support viral replication. Initiative 4 will involve support for a Data Analysis and Coordinating Center, which would support myriad activities.

Dr. Melillo explained that the Human Virome Program is envisioned as a 10-year program, but the current concept is focused on the first 5 years. She noted that the development of tools and methods will be focused on in the first phase of the program. Functional studies will be increasingly emphasized in the second phase. Cohort studies will occur in both phases, but the first phase will be limited to U.S. institutions. She briefly outlined the Phase 1 budget, which is $228.25 million over 5 years, distributed across the four initiatives.

Discussion Highlights

- The discussants, Drs. Jian-Dong Li and Gary Koretzky, provided their comments. Both discussants expressed support for the concept.
- Dr. Li asked whether the program will consider the effects of the other pathogens. Dr. Melillo responded that the topic of pathogenic viruses might be outside the program's scope. NIH ICs could pursue related questions in specific disease areas. Dr. Koretzky added that the nature of commensal relationships is not understood fully, and more exploration is needed.
- Dr. Melillo clarified the distribution of the proposed budget. Two receipt dates are anticipated; more funds are expected for the functional studies in Phase 2, but this increase has not been

projected in Phase 1. Dr. Becky Miller added that many of the tools and methods are expected to relate to bioinformatics, and those costs might be lower.

- Dr. Koretzky remarked that initiative 1 will be important but highly complex, and the RFA must be crafted carefully. He suggested frontloading initiative 2 to advance initiative 1 more efficiently. He added that the functional studies will be critical and suggested providing additional guidance in this area.
- When asked about methods for data sharing and use to ensure consistency with other efforts, Dr. Melillo noted that the Data Analysis and Coordinating Center will be focused on data harmonization and coordination. She added that the Center's standards will be essential. Additionally, the team will adapt lessons learned from the Human Microbiome Program.
- Council members suggested coordination with other CF initiatives compiling big data collections on well-defined, well-considered populations.
- In response to a suggestion to balance the budgets of initiatives 1 and 3 more evenly, Dr. Miller clarified that the program has considered using previously established cohorts to leverage previous effort, but baseline data still are needed. She emphasized the importance of establishing the initial characterizations of the virome. Council members remained uncertain about the budget balance, and Dr. Melillo agreed to take this point into consideration.
- Dr. Melillo confirmed that bacteriophages and human endogenous retroviruses would be considered part of the virome.
- Dr. Melillo agreed that establishment of animal models is likely to require extensive effort.

Vote

A motion to approve the Human Virome Program concept was forwarded and seconded. The motion passed with no abstentions.

VII. NEW CF CONCEPT CLEARANCE: ADVANCING HEALTH COMMUNICATION SCIENCE AND PRACTICE

William Klein, Ph.D., Associate Director, Behavioral Research Program, Division of Cancer Control and Population Sciences, NCI, introduced a new CF program entitled, "Advancing Health Communication Science and Practice", which aims to investigate, develop, test, and disseminate new approaches for effective and equitable health communication from basic discovery research through implementation, including measuring communication exposure and impact, addressing misinformation, engaging communities, and building trust. The budget for the concept is around $31 million per year for the first 5 years, with the program projected to run for 10 years.

Accurate health communication is necessary for providing health information to people so they can make health decisions. Recent research indicates a breakdown in health communication and a significant distrust in scientists, institutions, and health experts. COVID-19 deaths and hospitalizations have been exacerbated by misinformation and vaccine hesitancy, and the problem extends to other health areas. Although behavioral and social sciences research (BSSR) directly addressing key health communications has increased recently, human intuition about how to change others' behavior often is incorrect, and determining how to address rampant misinformation, requires robust social sciences.

Key gaps in health communication research were identified during planning activities with experts and stakeholders. These needs included community-engaged, timely, and useful communication research; research on the science of trust, particularly within diverse communities; improvements in health and

science literacy; research on the spread of health-related misinformation; innovative implementation structures and partnerships to promote equitable health communication; and workforce development for communicators and communication researchers. Since this topic applies across diseases and requires synergistic and crosscutting research, it is appropriate for the CF to support this important research topic. Health communication is underfunded across all ICs and topics, and traditional research models are inadequate—cyclical and iterative translational research often is required. This research will be transformative and catalytic to other areas of behavioral and biomedical science.

Christine Hunter, Ph.D., Acting Director, OBSSR, explained the three proposed initiatives. A research network will support ecologically valid, iterative learning cycle research projects across the translational continuum and disciplines to develop and test new health communication approaches that are sustainable and can be adopted by future health communication researchers in the broader BSSR fields. It will encourage diversity in the health communication workforce. The sub-initiative will be an opportunity to provide funds for rapid-response health communication research addressing new and emerging health communication challenges. Deliverables will be effective health communication approaches with a new understanding of what approaches work for whom, under what circumstances, and why, as well as a cadre of new health communication researchers from diverse backgrounds and disciplines. The network will support a full-cycle translational framework of basic research to test the basic mechanisms and processes that drive or inhibit communication, intervention research in early phases, and implementation research with an emphasis on real-world applicability and sustainability.

Research projects will develop and test innovative methods and measures of health communication exposure, impact, context, and predictors. They will assess the quality of information and partner with technology and social media platforms, marketing experts, and communicators of health information. Measures developed by this activity will be shared with and adopted by the full-cycle research activities, when appropriate, for additional testing and validation. Deliverables for this task are validated methods and measures for factors relevant to the current health communication ecosystem, including exposure to messages, misinformation, the impact of communication exposure, the spread of misinformation, health and science literacy, and other predictors of communication outcomes.

A coordination and dissemination center will offer consortium-wide efforts to foster collaborations, share results, address shared challenges, and facilitate cross-study learning. It will collect, compile, and disseminate evidence-based findings, approaches, and other resources from research and measurement initiatives. It will develop educational and training materials for health communication researchers and conduct active outreach to and technical assistance for various audiences, including health communication researchers and health communicators. It also will offer expert guidance in health equity and community-engaged research. Deliverables from this center will include a repository of evidence-based measures, tools, and other resources; active dissemination of best practices to health communication researchers and other audiences influenced by health communication research; and robust assessment of the uptake, use, and impact of all program resources.

Discussion Highlights

- The discussants, Drs. Edith Mitchell and Maria Rosario Araneta, provided their comments. Dr. Mitchell expressed strong support for the program, and Dr. Araneta concurred.
- In response to Dr. Mitchell's questions, Dr. Hunter explained that the team has been in contact with many other agencies conducting activities in this space, and partnership will be important to ensure that the initiative does not duplicate existing work. The team will leverage existing partnerships with social media and technology companies, as well as seek new partnerships. This will help address the evolving ecosystem of communication, in general, and health communication, in particular. Dr. Klein commented that although technology changes quickly,

basic human motivations and factors that drive behavior remain consistent over time, so many research projects funded by this initiative will be technology-agnostic. He added that opinion leaders are needed for effective communication, which may require seeking out individuals with community respect in religious settings or schools and giving them the tools to communicate information in impactful ways.

- Dr. Hunter explained that the research will include a focus on communicating standards of excellence, and the coordination and dissemination center will help disseminate the message. The initiative will synthesize behavior change outcomes, in addition to changes in knowledge and attitudes, but determining how to account for the multifactor nature of behavior change will require careful consideration.
- Dr. Araneta concurred with Dr. Mitchell's suggestions and emphasized that populations who are part of the digital divide are traditionally not represented in research. People who speak languages other than English often are at a disadvantage for health communication. Some individuals rely on information from the country they emigrated from, particularly information related to culturally familiar and personal interventions. She recommended an intentional attempt to engage new researchers from the communities under study and encouraged the participation of anthropologists. She also encouraged them to engage traditionally underrepresented communities. Dr. Araneta encouraged the team to use traditional media that are accessible to all in order to better understand the differences between passive communication and intentionally seeking health education information.
- In response to Dr. Araneta's questions, Dr. Hunter clarified that the team hopes to receive applications that address a wide spectrum of diseases and conditions. Although infectious diseases have been emphasized lately, health communication around chronic and long-standing public health issues also requires research. Dr. Klein commented that they will aim to connect with researchers who do not typically come to the NIH for funding—for example, in such areas as anthropology, computer science, demography, and other social sciences—because those researchers will be knowledgeable about communication and how information spreads.
- Council members encouraged the team to identify areas with the potential for direct impact to keep the scope manageable.
- When asked about developing new communication modalities, Dr. Hunter explained that shared funding opportunities can be challenging but productive. She noted that they have been engaged with the National Science Foundation (NSF) on their efforts.
- Dr. Hunter clarified that international members of the consortium would be welcome but have not been a focus.
- Council members commented that having clear outreach goals and gathering individuals who are unaware of or who have not sought NIH funding would be critical to amplify the program.

Vote

A motion to approve the Advancing Health Communication Science and Practice concept was forwarded and seconded. The motion passed with no abstentions.

VIII. NEW OBSSR CONCEPT CLEARANCE: ACCELERATING BEHAVIORAL AND SOCIAL SCIENCE THROUGH ONTOLOGY DEVELOPMENT AND USE

Dr. Hunter introduced a new OBSSR concept entitled, "Accelerating Behavioral and Social Science Through Ontology Development and Use", a 5-year cooperative agreement to support independent, but collaborative research projects focused on ontology development, dissemination, and use. The concept

also will support a coordinating center to foster collaborations, share results, address common challenges, and facilitate cross-project learning; provide ontology-related informatics expertise; and disseminate resources to support ontology development, uptake, and sustainable use.

BSSR findings have increased substantially, but the quantity and complexity of data is challenging to structure, mine, standardize, and integrate. Although the biomedical sciences have used semantic knowledge structures—such as controlled vocabularies, taxonomies, and ontologies—to represent the current state of knowledge and create data resources that are findable, accessible, interoperable, and reusable, the development and uptake of ontologies in BSSR has been challenged by lack of familiarity and common vocabularies. Aggregation is limited within and across domains, and theories, constructs, and measures have proliferated because there are more incentives to create new theories and constructs.

Ontologies are a systematic method for articulating a controlled vocabulary of agreed-upon terms, definitions, and representations of interrelationships. Ontologies must be machine-readable with well-defined semantics and must enumerate the types of concepts used and constraints on their use. The conceptualization must be agreed upon and accepted by those working in the discipline, and it must outline the relevant concepts and relationships among them that exist within a specific domain. Ontologies accelerate scientific advances by supporting transparent, reproducible, and replicable science and facilitate communication, comparison, and integration of discovery. They make domain assumptions explicit and support identification of conceptual and empirical inconsistencies, unanswered questions, and novel hypotheses. A shared understanding of the structure of information within a domain allows aggregation of knowledge within and across disciplines. Ontologies also enable the reuse of domain knowledge, such as enhanced meta-analyses.

No single method exists to build knowledge representation structures and ontologies; doing so requires informational or computational and domain expertise from beginning to end, and a single ontology might not work for all applications. A National Academies of Sciences, Engineering, and Medicine study concluded that ontology development and use has the potential to transform behavioral science into a more integrated domain, make evidence more searchable, and leverage technology to support the discovery of new relationships, the development of novel hypotheses, and the identification of knowledge gaps. Although ontologies are central to the advancement of science, no funding mechanisms exist to support the long-term development, dissemination, and maintenance of ontologies and related tools in the behavioral sciences.

Dr. Hunter outlined the proposed initiative structure. A coordination and dissemination center will foster collaboration, share results, address common challenges, and facilitate learning across projects by providing ontology-related computational and informatics technical expertise; compiling and disseminating lessons learned, best practices, and other resources to support ontology development, uptake, and sustainable use; and engage in active outreach to and coordination with relevant entities to increase the understanding of and demand for BSSR ontology-related content, tools, and resources. The research project network will support independent but collaborative research projects that will develop ontological content, resources, or tools; test innovative models of ontology development and refinement; plan for dissemination and sustainability; support multidisciplinary teams; and engage with end users. Deliverables for this concept include multiple sustainable research resources, such as enhanced ontological content and infrastructure for BSSR and technology platforms to facilitate data exchange and aggregation. The concept also will support advances in computational methodologies to develop and curate ontologies and tools and resources to support ontology dissemination, uptake, and sustained use. Grantees will also form professional networks to engage, inform, and build capacity for ontology use in BSSR more broadly.

Discussion Highlights

- The discussants, Drs. Kevin Johnson and Paul Kenny, provided their comments. Both were strongly supportive of the concept, which Dr. Johnson agreed was essential and based on solid plans. Dr. Johnson also pointed out the opportunity for work conducted under this concept to be catalyzed using intramurally funded researchers for sustainability.
- In response to Dr. Johnson's questions, Dr. Hunter explained that a single ontology likely will not be possible, but this project will look for iterative learning ontologies to connect with existing knowledge structures. Engaging international audiences will be critical to both supporting science and ensuring equity. Dr. Hunter acknowledged the difficulty of addressing artificial silos, which is likely to be an ongoing challenge for the project team.
- Dr. Kenny pointed out that this concept could immediately improve electronic health records. He emphasized the need to select research projects that can best facilitate identification ontologies that will be broadly accepted and widely implemented. Dr. Hunter agreed that the concept is designed to have maximal impact and require engagement with users.

Vote

A motion to approve the Accelerating Behavioral and Social Science Through Ontology Development and Use concept was forwarded and seconded. The motion passed with no abstentions.

IX. ADJOURNMENT FOR THE DAY

Dr. Eisinger adjourned the meeting at 3:28 p.m. on September 8, 2022.

Day 2

X. 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 meeting 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 142 ORIP applications with requested first-year direct costs of $685,460,579.

XI. CALL TO ORDER

Dr. Eisinger welcomed participants, NIH staff members, and members of the public to the second day of the meeting and reviewed the day's agenda. The open session of the virtual meeting began at 11:45 a.m. on Friday, September 9, 2022.

[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.

XII. ARPA-H: AN UPDATE

Adam H. Russell, D.Phil., Acting Deputy Director, ARPA-H, introduced ARPA-H by explaining that the Defense Advanced Research Projects Agency (DARPA) was created in response to the launch of the Sputnik satellite by the Soviet Union in 1957. This suggested that the United States was lagging in a competition for technological advancements. Other science and technology efforts were strengthened at the same time, creating an ecosystem model to support constant breakthroughs to support the scientific ecosystem.

Bringing the Advanced Research Projects Agency (ARPA) model to the health care system through ARPA-H will support the constant breakthroughs the U.S. health care research ecosystem needs. Advances in treatment for many conditions can be created through the combination of urgency and technology. Dr. Russell commented that a perpetual innovation cycle is needed to support the collective follow-through often lacking after individual breakthroughs. The ARPA-H mission is to create and accelerate high-impact health solutions for well-defined problems and empower every American to realize their health potential.

ARPA-H was developed as a system that balances mission- and requirements-driven aspects. Key themes identified in 250 stakeholder listening sessions include the need for ARPA-H to be complementary to the NIH, the importance of health equity and diversity, and the need to invest in capabilities that could create breakthroughs across many conditions and diseases. Dr. Russell commented that ARPA-H should make daring efforts to remove barriers currently challenging stakeholder progress. Listening session discussions also emphasized the importance of engaging stakeholders early and often to ensure projects are relevant and address concerns. The complex nature of health means multidisciplinary partnerships will be important. Dr. Russell directed attendees to the report released by the Office of Science and Technology Policy for more information on the listening sessions.

Since agility will be key to the ARPA-H character, hiring practices will be nontraditional, such as limited terms for program managers to ensure regular integration of new perspectives. ARPA-H program managers will be mission-oriented civil servants who can work quickly and creatively on time-limited projects. They develop programs through a rigorous ideation process using the Heilmeier Questions. Broad. B and flexible funding and an exemption from traditional NIH review processes will be required for ARPA-H to support risky, but potentially high-impact strategies and projects.

The $1 billion appropriated in FY 2022 to ARPA-H must be distributed before the end of September 2024, but the inaugural director has not yet been appointed. The location of ARPA-H within NIH allows existing infrastructure to be used to create ARPA-H quickly; however, it will be unique by nature of its mission and structure. The director will have a 5-year term and will recruit and empower program managers to execute programs and fulfill ARPA-H's vision. Dr. Russell emphasized that program managers, rather than higher-level managers, will drive many of ARPA-H's processes. He reiterated that innovation requires a landscape, rather than a linear process, for the best ideas to emerge, be tested, refined, and promoted and developed quickly when successful. The program managers will drive the intellectual capital, goals, and visions of the programs and will be provided significant resources and support. Dr. Russell commented that program managers must be driven by the mission because the methods needed to reach ARPA-H's goals are the unknown aspect of this process. ARPA-H is structured with minimal bureaucracy to ensure agility, as such it will require advocates to ensure it retains the independence and autonomy needed to fulfill its mission.

The high-uncertainty, high-return approach is critical to the ARPA-H model. As risk-taking is necessary for the ARPA model to be successful, its culture is designed to promote big thinking and taking big bets by removing the fear of failure. Program managers will ensure that researchers are informed, guide

projects to change direction when necessary, and increase support for more successful projects. To avoid duplicating current research efforts, program managers must sufficiently address the Heilmeier Questions, which includes detailing how others are addressing the problem and what technical limitations their approaches face that are preventing them from solving it today. ARPA-H is adding components to help create equitable outcomes and solutions that are reproducible, a quality many innovations lack and one that is critical to health care. One method to design reproducible solutions is to integrate metascience, testing, and evaluation from the beginning of the process, ensuring that failures can be understood.

Dr. Russell emphasized the importance of countering the preconception that "quick wins" are critical for success, noting that any problems ARPA-H solves immediately are not examples of the strengths of this model. Transparency is required to communicate this idea and keep people excited about the potential for ARPA-H's strategies to be successful. Example areas in which ARPA-H could work include methods to turn data into knowledge, innovations in treatment platforms, health protection and forecasting strategies, resilient systems, process innovations, and scale and equity. Dr. Russell noted that the first test of the internet (then the ARPAnet) was only partially successful. He proposed that ARPA-H was similarly on track for long-term success.

Discussion Highlights

- Dr. Russell clarified that existing organizations with similar missions serve their own customer bases, but ARPA-H will remain in close communication with them about potential crossovers. He reiterated that program managers, in answering the Heilmeier Questions, will conduct market research on current efforts, including both public and private health care technology projects, and identify any tradeoffs preventing success that ARPA-H could address. Individual programs will have significant control over their area of research, and ARPA-H will support projects that can address a problem across many conditions.
- When asked how the awards will foster ideas from the research community rather than from program managers, Dr. Russell explained that ARPA-H seeks program managers who propose compelling problems, allowing ARPA-H to fund many creative approaches to potential solutions. He clarified that program managers will identify promising programs, then pitch those ideas to the director, who will ultimately decide which to fund. He emphasized that, in addition to having to credibly and convincingly answer the Heilmeier Questions, all program ideas will be vetted by experts before the director approves them. He encouraged nominations of program managers.
- Dr. Russell provided examples of problems solved through the ARPA mechanism, such as the creation of stealth aircraft, an idea initially rejected by the Air Force as too disruptive to existing processes, as well as the early stages of the mRNA technology later used for COVID-19 vaccines. He commented that ARPAs demonstrate unimagined and seemingly impossible futures. Council members recommended that ARPA-H publicize such examples frequently to demonstrate ARPA-H's capabilities more concretely.
- In response to a question about using large data sets to identify real-world problems, Dr. Russell stated that he expects ARPA-H will have programs in the big health data space and anticipates activities that will leverage data to both help better understand problems as well as enable solutions.

XIII. CF CONCEPT CLEARANCE: CF DATA ECOSYSTEM (CFDE) PHASE 2

Chris Kinsinger, Ph.D., Assistant Director for Catalytic Resources, OSC, presented on the Phase 2 concept clearance for CFDE, a unique program that aims to increase the impact of existing CF program data. CFDE enables users to query across and use multiple CF data sets managed by independent data coordinating centers (DCCs). CFDE also aims to conduct training and outreach to increase the use of CF

data sets and help researchers learn how to work with data in the cloud. CFDE will coordinate and integrate infrastructure and activities into a cohesive ecosystem with its own Integration and Coordination Center.

The CFDE Council of Councils Working Group report, presented at the May 2022 Council meeting, recommended continuation of CFDE based on its important goals, substantial initial progress, and solid foundation for future work. CFDE's challenges are common to data science. Although some are beyond CFDE's immediate control, CFDE will work with the broader community to expand interoperability. The working group recommended that CFDE advance the transition to cloud computing by increasing and diversifying its training and outreach initiatives. The chief metric of success for CFDE is discovery—if CFDE is successful, many investigators will use CF data for new discoveries and new purposes.

Dr. Kinsinger outlined one example of success within the 3-year CFDE pilot that required investigators to review gene expression in neuroblastoma cohorts and normal tissues in two different CF data sets, resulting in identification of an immunotherapy target. He pointed out that the majority of the time required to identify this gene was spent "wrangling" data. CF programs generally harmonize their data within the program, but the data often are processed differently between programs. Combining data from different programs requires running raw data through a common analysis pipeline to reanalyze and reassemble the data, which can be time consuming and costly. The output often can be analyzed only by highly skilled bioinformaticians.

CFDE has been working to overcome these barriers. To improve findability, CFDE developed a search portal aggregating descriptions of data from 11 CF programs, allowing end users to look for data sets. The portal then connects the user to the data via a cloud workspace, eliminating the need for a local download and the associated resources required. To improve harmonization and analysis, CFDE established a common pipeline on the cloud. Few investigators are comfortable with programming environments, so the CFDE team converted analysis scripts into mobile apps, making bioinformatic analysis of tabulated data easier. Dr. Kinsinger emphasized that CFDE's work has allowed anyone in the world with a laptop, internet connection, and CF data access to conduct analyses easily.

CFDE proposes a plan with five interconnected initiatives: a knowledge portal, a data resource portal, the cloud workspace, a Center for Training, and an Integration and Coordination Center. CFDE will continue to engage with DCCs to enhance findability and accessibility of CF data through an expanded portal that will direct users to data or knowledge searches, with a flexible design to support new data types. CFDE will add features to NIH's existing cloud workspaces to make them more interoperable with CF data sets and will work closely with ODSS on this initiative. A variety of training and outreach activities will be necessary to support the paradigm shift to cloud computing, and a Center for Training will be established to conduct a landscape analysis of unmet needs and evaluate the effectiveness of training and outreach activities. The Integration and Coordination Center will ensure internal cohesion across CFDE by tracking tasks, helping CF programs identify repositories for long-term sustainability, and conducting regular internal evaluations.

The proposed budget of $23 million per year for 5 years includes the components discussed, continued support for DCC engagement, and research management support. Dr. Kinsinger noted that although most components are budgeted at the same levels as the pilot phase, the budget for training and outreach has been increased by $5 million per year.

Discussion Highlights

- The discussants, Drs. Horwitz and Sachin Kheterpal, provided their comments. Both strongly supported the Phase 2 proposal, which Dr. Horwitz confirmed addressed the working group's recommendations well. Dr. Horwitz noted that CFDE will address challenges that affect many

data sets and emphasized that the plans for scalable training and cloud computing will improve research equity.

- Dr. Kheterpal recommended allocating funds to support reassessing and transitioning technologies that will have changed over 5 years and asked about the DCC engagement budget. Dr. Kinsinger explained that DCCs will be transitioned to other funding when the program ends. DCC engagement funding was necessary during the CFDE pilot phase because those activities were not funded by the DCCs' RFAs, but DCC engagement with CFDE now can be incorporated into parent awards. He noted that data types compliant with CFDE will become more common as CFDE becomes more established. The budget projects a steady amount over 5 years to support adding new DCCs.
- When asked whether CFDE has conducted an ecosystem evaluation to understand what other large data repositories could be integrated, Dr. Kinsinger clarified that CFDE's mission is centered on CF programs, which use a wide variety of data types. He reiterated that the CFDE focuses on connecting data where they are and bringing users to them. ODSS may be engaged to help identify appropriate data sets outside the CF.

Vote

A motion to approve the CFDE Phase 2 concept was forwarded and seconded. The motion passed with no abstentions.

XIV. CF CONCEPT CLEARANCE: REISSUE OF MOLECULAR TRANSDUCERS OF PHYSICAL ACTIVITY (MoTrPAc) RFAS

Richard Hodes, M.D., Director, NIA, presented for concept clearance the reissue of MoTrPAc RFAs. The objective of this CF program is to better understand the mechanisms by which the effects of exercise are transmitted and translated to multiple organs and tissues of the body, in addition to identifying variables that affect this signaling, including age, sex, genotype, and body composition. The ultimate aim of the initiative is to help maximize the benefits of exercise to promote increased health and well-being. The program comprises five components: clinical centers, preclinical animal studies, multiomic analysis sites, a bioinformatic core, and a coordinating center. The proposal includes a request for an additional $51 million over the next 4 years.

Dr. Hodes reviewed the design of the MoTrPAc studies. Preclinical studies involved young and aged rats that were studied before and after exposure to acute bouts of endurance exercise or a long-term exercise training regimen. Human clinical studies involved both pediatric and adult cohorts. Both sedentary and active adults were studied for their response to acute endurance and strength testing, as well as for their response to a longer training period. The pediatric group also was divided into low-active and high-active groups, which were assessed for their responses to acute exercise.

Dr. Hodes provided an update on the clinical studies, which were planned in 2019 and profoundly delayed by the COVID-19 pandemic, which resulted in the temporary shutdown of many program-related activities. Dr. Hodes confirmed that, in recent months, the MoTrPAc program sites have resumed their activities. Full recruitment is projected to be achieved by December 2024, the clinical protocol will be completed in 2025, and data generation and analysis will continue through 2026. To ensure continuity in the implementation of the program, the reissue proposal includes a limited competition renewal for current clinical sites and the coordinating center.

Dr. Hodes described results of the preclinical studies. Initially, the animal research only included endurance studies of 6-month-old and 18-month-old rats. These studies are partly concluded. Dr. Hodes noted that no resistance exercise protocols were included in the program because none had been validated

sufficiently. Since that time of initiation, however, the laboratory of Dr. Sue Bodine at the University of Iowa Carver College of Medicine has documented a reliable resistance ladder-climbing task that has been incorporated in the preclinical study protocols. Preliminary fundings of the studies—which have involved measurements of more than 40,000 biological analytes—have identified several pathways that respond to acute exercise or across the trajectory of a training period. Striking sex-specific responses to exercise have been documented, with the majority of molecular clusters having different trajectories in male and female animals. These data will be collected in a database available for use by the scientific community. The MoTrPAc continuation request includes a limited competition renewal for preclinical sites involved in the studies, as well as an open competition for a limited number of studies. The open competition is intended to kick-start a community-wide effort that hopefully will extend beyond the completion of the MoTrPAc program.

Reviewing the proposed budget for the reissue request, Dr. Hodes noted that carryover funds from the initial program will still be available in fiscal years (FYs) 2023 and 2024. Funding for the coordinating center and clinical sites will continue through FY 2025 and taper off in FY 2026, as data accrual and clinical activities wane. The multiomic sites, working with forthcoming samples from human and animal studies, are projected to continue their activities well into 2026. The rat endurance studies, mechanistic studies, open competition, and bioinformatics center also will continue their activities throughout the funding period. To ensure ongoing support beyond the MoTrPAc program, the data resulting from MoTrPAc activities will be incorporated into CFDE.

Discussion Highlights

- The discussants, Drs. Araneta and Jean Schaffer, provided their comments. Both expressed enthusiastic support for the program. Dr. Schaffer noted that the bioinformatics group would be well positioned to help the wider scientific community overcome accessibility barriers to MoTrPAc data.
- In response to Dr. Schaffer's question, Dr. Hodes explained that the bioinformatics site will respond to increased amounts of data that are generated and increased demand for access to these data. He welcomed feedback from the scientific community regarding accessibility of the data and noted that the program would benefit from proactively soliciting this input.
- Dr. Schaffer inquired about the long-term management of biological samples generated by the program and asked about the program's rebound after the COVID-19 pandemic and contingency plans for possible work stoppages in the future. Dr. Hodes discussed the challenges associated with prioritizing the use of valuable biological samples. He thanked Dr. Schaffer for her suggestion of training expert investigators in standardized protocols to be capable of generating such samples and making them available to the wider community. Dr. Hodes added that many lessons have been learned regarding program activities during the COVID-19 pandemic and that these lessons would inform the response to any future pandemiclike events.
- In response to Dr. Araneta's questions, Dr. Hodes commented that all animals used in the preclinical studies were nulliparous and added that the proposed open competition would provide an opportunity for further longitudinal studies that might reveal "legacy effects" of exercise interventions.
- When asked about the diversity of the human cohort in terms of age, ethnicity, race, and comorbidities, Dr. Hodes answered that close attention had been paid to the diversity of the human population that was studied. Life histories and questionnaires are being used to address heterogeneity in individual study subjects that cannot be controlled for in groups.

- In response to a question about using results from the animal studies to inform the clinical studies, Dr. Hodes noted that the sexual dimorphism observed in the preclinical studies would not have much effect on the human studies because the human cohorts already were balanced in terms of sex. He added that pathways and tissues that were observed to be of interest in animals would be further scrutinized in the human data.

Vote

A motion to approve the reissue of the MoTrPAc concept was forwarded and seconded. The motion passed with one abstention.

XV. NEW *ALL OF US* CONCEPT: R03/R21 TO STIMULATE NOVEL ANALYSES USING *ALL OF US* RESEARCH PROGRAM DATA

Sheri Schully, Ph.D., Deputy Chief Medical and Scientific Officer, *All of Us* Research Program, presented a new concept entitled, "Trans-NIH Small Grants Program (R03/R21) to Stimulate Novel Analyses Using *All of Us* Research Program Data". The objective of the proposed program is to advance research in high-priority ICO mission areas by stimulating novel analyses and tool development using *All of Us* Research Program data. The R03 funding mechanism would be used to analyze data using standard tools, and the R21 funding mechanism would be used to develop new tools, use of the tools to analyze data, and make the tools available. The *All of Us* Research Program is setting aside $2 million for 10 awards, and ICOs can use their own funds for additional awards. The award period will be 2 years.

The mission of the *All of Us* Research Program is to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care. *All of Us* is achieving this mission by striving to (1) nurture partnerships for decades with at least 1 million participants who reflect the broad diversity in the United States; (2) deliver one of the largest, richest biomedical data sets that is broadly available and secure; and (3) catalyze an ecosystem of communities, researchers, and funders who will make *All of Us* an indispensable part of health research.

The *All of Us* database currently includes survey responses from more than 372,000 participants, more than 80 percent of whom are from populations that have been underrepresented in biomedical research and more than 50 percent of whom are of racial and ethnic minorities. The participants also reflect high diversity in regard to geography and age. The Researcher Workbench includes 306,000 physical measurements, 258,000 electronic health records, 165,000 genotyping arrays, 100,000 whole-genome sequences, and 12,000 Fitbit records. Dr. Schully noted that additional data will be added in the winter of 2022.

In December 2021, the *All of Us* Trans-NIH Liaisons Coordinating Committee Team recommended that the program facilitate the analysis of using its data in a two-pronged approach: (1) provide administrative supplements to existing awards and (2) solicit new grant applications. A group of 22 IC Directors enthusiastically endorsed this approach. During Phase 1, which was implemented in FY 2022, 29 ICOs signed onto a Notice of Special Interest for administrative supplements to analyze *All of Us* data, and 23 supplements were awarded across 15 ICOs. Phase 2, which will be implemented in FY 2023, will stimulate new grant applications to analyze data, develop new analytical tools, and make the tools broadly available. To date, 23 ICOs have expressed interest in signing on to the R03 RFA, and 27 ICOs have expressed interest in signing on to the R21 RFA.

Discussion Highlights

- The discussants, Drs. Scout and Schaffer, provided their comments. Both discussants expressed support for the concept. Dr. Scout remarked on the diversity of resources supported through the

All of Us Research Program. He noted that the program already has obtained investments from numerous ICOs. Dr. Scout also highlighted efforts to create public data sets through the program.

- Dr. Scout commented that the small grant structure will support early-stage and underrepresented investigators and will provide new tools. He asked about strategies to ensure underrepresented investigators are provided access to Researcher Workbench. Dr. Schully explained that the program has engaged with minority-serving institutions and has provided support (e.g., free credits) for accessing this resource. Additionally, a diversity supplement notice will be released in FY 2023.
- Dr. Schaffer inquired about the development of webinars detailing the use of Researcher Workbench, as well as a mechanism for addressing unresolved questions. Dr. Schully explained that the program has published YouTube videos with walkthroughs on the use of Researcher Workbench. Additionally, the program staff hold office hours to engage with users and answer questions.
- Dr. Schaffer commented that statistical challenges related to new biological discoveries within diverse populations might emerge within the supported projects. She asked whether proposals related to select subpopulations would be considered. Dr. Schully responded that the awards could be focused on subpopulations, and the program is working closely with subject matter experts at the involved NIH ICs to implement the awards.
- Dr. Schaffer remarked that the data resource will grow over time. She asked how the program will leverage the initial investments to encourage more in-depth analyses within the populations. Dr. Schully responded that the program will engage with awardees to share lessons learned and foster collaborations.
- In response to a question about the incorporation of questions about physical, sexual, and emotional abuse and childhood neglect in *All of Us*, Dr. Schully explained that the program is developing a mental health and well-being module that will be released in the winter of 2023 Council members recommended both making the questions as specific as possible, because participants may be hesitant to discuss these factors, and considering current exposure to violence and coordinating with the Adolescent Brain Cognitive Development (ABCD) Study®.
- Dr. Schully confirmed that the program team is considering how to ensure tools developed through the program are sustainable. She noted that coordination with R21 grantees and IC partners will be needed.

Vote

A motion to approve the Trans-NIH Small Grants Program (R03/R21) to Stimulate Novel Analyses Using *All of Us* Research Program Data concept was forwarded and seconded. The motion passed with no abstentions.

XVI. NEW ONR CONCEPT: FOOD AS MEDICINE NETWORKS OR CENTERS OF EXCELLENCE

Christopher Lynch, Ph.D., Acting Director, ONR, introduced a new concept for Food as Medicine Networks or Centers of Excellence, which will support interventional, implementation, behavioral science, and health quality research to reduce the burden of diet-related diseases and nutrition disparities using Food as Medicine and other approaches. The concept will use health centers or networks as the nexus of activity and agent of change in their own communities and health systems. The anticipated number of awards is contingent upon NIH appropriation of $20 million per year and submission of meritorious applications. The concept will be structured in phases—the planning and pilot phase will

support up to 10 awards for 3 years, leading to competition for the study period of up to five awards for 5 years.

Obesity and other diet-related chronic diseases are highly prevalent in the United States, and rates are increasing. Research suggests that more than 96 percent of the population with obesity has unmet care needs. Community and environmental factors confound treatment outcomes, and risks for obesity and related comorbidities are higher in adverse social circumstances. Within communities, coordinating responses among authorities is extremely difficult. Hunger levels have been rising; food insecurity is linked to poverty and is far higher in households of minority populations and those with children, and it has many health, behavioral, and social consequences. Additionally, malnutrition in clinical settings affects more than 30 percent of hospitalized patients and is associated with high mortality and morbidity, functional decline, prolonged hospital stays, and increased health care costs, as well as increased readmittance to hospitals. Training and reimbursement for lifestyle medicine, nutrition, behavioral counseling, and therapeutics that would address these issues is inadequate.

This concept aims to use Food as Medicine to address these problems. Food as Medicine programs respond to the critical link between diet and health by providing healthy food and connections between the health care system and patient communities. Health care providers are recognized as a trusted source of information, and Food as Medicine programs have been shown to address hunger, food insecurity, and unhealthy eating. This concept proposes that networks or centers of excellence used as a nexus for Food as Medicine activities also can investigate innovative approaches to address the systemic barriers that challenge interventions for obesity, diet-related chronic diseases, and disease-related malnutrition.

Dr. Lynch provided examples of research that could occur under this concept. Within academic health centers, nutrition-related training could be increased, and screening for malnutrition and food insecurity could be implemented at patient touch points and as part of community outreach. These centers also could perform health quality research to secure reimbursement for diet-related chronic disease care. The number of staff dieticians and medical social workers could be increased, and culinary medicine programs could be implemented. In the community, health networks or centers could facilitate better coordination with other community groups to improve nutrition-related issues.

The program deliverables could include common evaluation metrics that can measure the effect of Food as Medicine interventions on health conditions in the community; evidence-based diagnostic instruments and treatments for malnutrition in clinical settings to improve health care quality, treatment outcomes, and wellness; a profile of people who would benefit from different Food as Medicine interventions, in what ways, and under what circumstances; and an evidence base on relevant statistics to motivate policy change and uptake of interventions by the health care industry, insurers, and policymakers. ONR would convene annual meetings to showcase innovation in health systems and communities, as well as regionally appropriate and culturally sensitive Food as Medicine best practices.

Discussion Highlights

- The discussants, Drs. Patricia Hurn and Charles Mouton, provided their comments. Dr. Hurn agreed that the target is significant for the United States and other wealthy countries, the need is compelling, and the intent to create networks is pitched in the right place. The plan to address diet-related chronic disease early in life and in communities is well poised, and the interventional studies and proposed research are designed as a logical fit for NIH's strengths. The goals and deliverables also are practical and likely to have an impact, and the phased competition allows the research community time and experience to create and advance the proposed networks.
- Dr. Hurn highlighted several areas of concern, such as a lack of articulation between health network activities in the community and any activities where community members receive health

care and education (i.e., in health care systems, clinics, and hospitals), particularly how community issues influence research and what happens in the health care settings. Another concern is the lack of training for health care providers in nutrition, motivational interviewing, and behavioral interventions. She pointed out that the concept was specific to physicians, but the scope needs to be broadened in a multidisciplinary way, particularly because many individuals will receive care from multiple providers and some of those providers will not be physicians (e.g., pharmacists, social workers, nutrition science professionals, etc.). Grants supporting training and education are not outlined in the concept, so more specificity is needed about how training will be expanded.

- Dr. Lynch explained that nurses are very interested in participating and would be included in the program and agreed with the importance of including pharmacists. He stated that ideally, the concept would not be prescriptive, so investigators could determine how best to increase nutrition education in medical schools. He pointed out that relevant interventions often are disregarded because of low reimbursement rates, and centers will need to identify how to address the dismissive culture within their own health systems. Using a network approach will allow applicants to find opportunities within their community that would be most effective for improving health (e.g., attending health fairs, offering health education tailored to community needs), and health care systems often can use strategies that are not available to federal partners, such as raising funds from outside partners.
- Dr. Mouton agreed with Dr. Hurn's comments and highlighted two additional strengths: the focus on socioeconomic forces that affect treatment and health outcomes beyond nutrition and the effort to address lifestyle factors to facilitate care delivery. Dr. Mouton pointed out that some agencies currently engaged in community efforts related to nutrition and food, such as USDA and the Health Resources and Services Administration (HRSA), are not involved in the concept, which may affect whether the program can achieve its goals. He recommended asking all respondents to not only create centers within their health systems, but also use community engagement strategies.
- Dr. Mouton pointed out that many aspects of nutrition and eating behaviors are tied to culturally based behaviors, and how this initiative would address such barriers is unclear. He noted that the concept of Food as Medicine, if applied within health systems, may become focused too narrowly on food as therapeutics, so he recommended increased clarity or a name change related to that idea.
- Dr. Lynch explained that the vision for the concept includes researchers' contacting groups working within their communities—such as HRSA, USDA, and other programs—and organizing collaborations at the local level. Additionally, a local-level Food as Medicine program has the potential to be culturally and geographically sensitive. Dr. Mouton suggested that the concept requires either a narrower focus or engagement of a broader group of constituents to address all the pieces of this ambitious initiative without reinforcing existing silos between disciplines. Dr. Lynch commented that investigators will propose innovations to surmount those barriers. He added that although the initial investment is small, the program could be expanded if successful, adding that he hopes that communities will begin requesting centers in their areas, as happened with the NCI-Designated Cancer Centers program.
- Council members applauded the inclusion of microlevel systems to connect with community stakeholders and recommended adding macrolevel strategies to support these activities from multiple perspectives. When asked about plans to disseminate research results beyond the scope of NIH to achieve results with stakeholders, Dr. Lynch explained that researchers will be expected to publish the outcomes of their studies in peer-reviewed journals. An upcoming White House conference on Food as Medicine will provide the opportunity to engage other agencies

(e.g., U.S. Department of Housing and Urban Development, Centers for Medicare & Medicaid Services, Agency for Healthcare Research and Quality), and ONR could facilitate further engagement as needed to expand the initiative. Council members pointed out that common data sets and metrics can be promoted to help disseminate the research and increase connections between health systems.

- Drs. Hurn and Mouton recommended that Dr. Lynch refine the concept and return to the Council after the White House conference with clearer areas of concentration, particularly as related to the concerns raised in discussion. Dr. Eisinger confirmed that the Council would not vote on the concept at this time, but would revisit the concept at the January 2023 meeting.

XVII. VOTE ON COUNCIL OF COUNCILS OPERATING PROCEDURES

Dr. Eisinger explained that no revisions to the operating procedures have been requested.

Vote

A motion to approve the Council of Councils Operating Procedures was forwarded and seconded. The motion passed with no abstentions.

XVIII. DISCUSSION OF MEETING FORMAT

Dr. Eisinger recognized the value of meeting in person, but he explained that resumption of in-person meetings would be decided at the NIH leadership level and apply to all NIH advisory councils and study sections. A decision on the format of the January 2023 meeting has not been communicated. Council members discussed the merits and challenges of hybrid meetings, which can provide more options for participants, but must be designed carefully to ensure that all participants can engage equally.

Dr. Grieder noted that public comments sent to her in advance were shared with the Council in the e-book, but no Council action is needed.

XIX. CLOSING REMARKS

Dr. Eisinger thanked the participants and reminded them that the format of the January 2023 meeting will be confirmed at a later date.

XX. ADJOURNMENT

Dr. Eisinger adjourned the meeting at 3:14 p.m. on September 9, 2022.

XXI. CERTIFICATION

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

Robert W. Eisinger -S
Digitally signed by Robert W. Eisinger -S
Date: 2023.01.09 17:18:55 -05'00'

01-09-2023

Robert W. Eisinger, Ph.D.
Chair, NIH Council of Councils
Acting Director, DPCPSI, OD, NIH

Date

Franziska B. Grieder -S
Digitally signed by Franziska B. Grieder -S
Date: 2023.01.09 11:36:13 -05'00'

01-09-2023

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

Date