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

Council of Councils Meeting
May 14, 2013

Meeting Minutes

I. WELCOME

James M. Anderson, M.D., Ph.D., Chair, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. The meeting opened at 8:30 a.m. on Tuesday, May 14, 2013, in Building 31, 6th Floor, Room 10, on the NIH Campus, Bethesda, Maryland.

Dr. Anderson announced that the new members' appointments had been approved and that they can participate fully in the meeting. He also noted that members Drs. Brown, DeKosky, Guthrie, Lyerly, Murphy, and Rabinovich would be absent. Dr. Peter Hotez participated by teleconference. Following introductions and announcements from Robin I. Kawazoe, Executive Secretary of the Council of Councils, Dr. Anderson reviewed the day's agenda.

A. Attendance

1) Council Members Present

Chair: JAMES M. ANDERSON, M.D., PH.D., Director, DPCPSI, OD, NIH
Executive Secretary: ROBIN I. KAWAZOE, DPCPSI, OD, NIH
LAVARNE A. BURTON, M.A., American Kidney Fund, Rockville, MD
CARLOS D. BUSTAMANTE, PH.D., Stanford University School of Medicine, Stanford, CA
F. XAVIER CASTELLANOS, M.D., New York University of School of Medicine, New York, NY
JANICE E. CLEMENTS, PH.D., The Johns Hopkins University School of Medicine, Baltimore, MD
RICHARD L. EHMAN, M.D., Mayo Clinic College of Medicine, Rochester, MN
JACK A. ELIAS, M.D., Yale University School of Medicine, New Haven, CT
SUSAN F. GOEKLER, PH.D., M.C.H.E.S., Directors of Health Promotion and Education
RICHARD M. GREENWALD, PH.D., Simbex, iWalk, Thayer School of Engineering, Lebanon, NH
NANCY L. HAIGWOOD, PH.D., Oregon Health & Science University, Beaverton, OR

PETER J. HOTEZ, M.D., PH.D., Baylor College of Medicine, Houston, TX (via teleconference)
JEFFREY A. KAUFMAN, M.B.A., Adenoid Cystic Carcinoma Research Foundation, Needham, MA
GRACE LEMASTERS, PH.D., University of Cincinnati College of Medicine, Cincinnati, OH
MARK O. LIVELY, PH.D., Wake Forest University School of Medicine, Winston-Salem, NC
K.C. KENT LLOYD, D.V.M., PH.D., University of California, Davis, Davis, CA
CRAIG J. MCCLAIN, M.D., University of Louisville School of Medicine, Louisville, KY
JOYCE A. MITCHELL, PH.D. F.A.C.M.G., F.A.C.M.I., University of Utah, Salt Lake City, UT
REGIS O'KEEFE, M.D., PH.D., University of Rochester Medical Center, Rochester, NY
JAMES E. SCHWOB, M.D., PH.D., Tufts University School of Medicine, Boston, MA
TERRIE (FOX) WETLE, PH.D., Brown University Medical School, Providence, RI
GILBERT C. WHITE, II, M.D., Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI

Council Members Absent

EMERY N. BROWN, M.D., PH.D., Massachusetts Institute of Technology, Harvard Medical School, Massachusetts General Hospital, Cambridge, MA
STEVEN T. DEKOSKY, M.D., University of Virginia, Charlottesville, VA
BARBARA J. GUTHRIE, R.N., PH.D., F.A.A.N., Yale University, New Haven, CT
H. KIM LYERLY, M.D., Duke University School of Medicine, Durham, NC
ROBERT F. MURPHY, PH.D., Carnegie Mellon University, Pittsburgh, PA
REGINA RABINOVICH, M.D., Global Health Consultant, Seattle, WA

2)Liaisons

JANINE A. CLAYTON, M.D., Director, Office of Research on Women's Health, DPCPSI, OD
ROBERT EISINGER, PH.D., Director, Scientific and Program Operations, Office of AIDS Research, DPCPSI, OD (representing OAR Director, Jack Whitescarver, Ph.D.)
FRANZISKA B. GRIEDER, D.V.M., PH.D., Director, Office of Research Infrastructure Programs, DPCPSI, OD
ROBERT M. KAPLAN, PH.D., Director, Office of Behavioral and Social Sciences Research, DPCPSI, OD
DAVID M. MURRAY, PH.D., Director, Office of Disease Prevention (ODP), DPCPSI, OD

ELIZABETH L. WILDER, PH.D., Director, Office of Strategic Coordination, DPCPSI, OD

3) Ex Officio Member

LAWRENCE A. TABAK, D.D.S., PH.D., Principal Deputy Director, NIH (absent)

4) Presenters

FRANCIS S. COLLINS, M.D., PH.D., Director, NIH

OLEG MIROCHNITCHENKO, PH.D., Health Scientist Administrator, Division of Comparative Medicine, ORIP, DPCPSI, OD

JOHN SATTERLEE, PH.D., Program Director, National Institute on Drug Abuse

JOHN STAMATOYANNOPOULOS, M.D., Associate Professor of Genome Sciences and Medicine, University of Washington

5) NIH Staff and Guests

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

B. Meeting Procedures

Ms. Robin Kawazoe reviewed the following:

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

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

- Time has been allotted for discussion between the Council and presenters, but time for comments from other meeting attendees is limited. The public can submit comments in writing; instructions are available in the *Federal Register* notice for the meeting published on April 5, 2013.

- Council members should not speak on the Council's behalf or on activities not yet cleared by Council.

- Approved meeting minutes will be posted on the DPCPSI Web site.

C. Future Meeting Dates

The next Council meeting will be held on September 24, 2013. Council meetings in 2014 will be held on January 31, June 20, and September 5.

Council meetings in 2015 will be held on January 30, June 19, and September 1.

II. DPCPSI UPDATE

Dr. Anderson reported that NIH is operating at a program level of $29.15 billion for FY 2013, representing a 5% decrease from FY 2012 as a result of the continuing resolution and sequester. As a result, funding levels for non-competing (type 5) grants will be lower than committed levels. In addition, NIH will keep the average size of competing awards for FY 2013 similar to that for awards made in FY 2012, meaning the fewer awards will be granted, and inflationary increases for future-year commitments have been discontinued for all awards issued in FY 2013. The salary limits on grants, cooperative agreements, and contracts will continue. Dr. Anderson reported that NIH remains committed to protecting the pipeline of investigators; thus, the new investigator policies that are in place will be retained.

Education in science, technology, engineering, and mathematics (STEM) continues to be crucial to an educated public that can drive the economy forward. Thus STEM education has been established in the President's budget as a clear direction. Dr. Anderson noted, however, that the Federal government's approach to STEM education has been under scrutiny. In the America Competes Reauthorization Act of 2010, Congress called for the establishment of a National Science and Technology Committee on STEM Education (COSTEM) that would coordinate STEM education activities across the Federal government. In response to this charge, COSTEM conducted an inventory, using a broad definition of STEM education. Dr. Anderson noted that NIH makes a distinction between K-12 STEM activities and postdoctoral research fellowships. NIH considers the later to be a crucial activity for producing a specialized workforce and critical for its mission.

The COSTEM inventory, completed in late 2012, identified 220 STEM education programs accounting for $556 million. The Committee found little duplication across the programs, but it also found little coordination. COSTEM also was asked to develop a strategic plan, which is due to be released in a few weeks. In the meantime, the President's FY 2014 budget proposes a reorganization of Federal STEM education activities, including consolidation of 78 programs, which total $176.4 million, across nine Federal agencies. These include nine STEM education programs at NIH, accounting for $27.6 million. Three of these programs are housed in OD: the NIH Science Education Partnership Award (SEPA), the Office of Science Education Curriculum Supplement Series, and the Office of Science Education K-12 Program.

The budget proposes that these programs be unfunded in FY14 and beyond and their activities be coordinated with three lead agencies:

- The Smithsonian Institution, which will focus on curriculum development and the development of materials to engage the public.
- The National Science Foundation, which will focus on undergraduate education in STEM and a national strategy for fellowships.
- The U.S. Department of Education, which will focus on K-12 education.

This change aligns with these agencies' areas of focus.

Dr. Anderson noted that although these three agencies will serve as leads, they will continue to look to other agencies to assist in developing content for their educational programs and provide access to infrastructure that will facilitate educational and content development efforts.

Because the future is unclear, NIH has paused its funding of new K-12 STEM education grants and contracts in FY 2013, and the SEPA program announcement, which expired in June 2012, will not be renewed. Non-competing projects will be awarded in FY 2013, and will be subject to the reductions all grants face because of sequestration. Decisions on funding for non-competing projects in FY 2014 and beyond will be left to the discretion of the Institutes and Offices. Dr. Anderson noted that NIH expects additional guidance within the next few weeks with respect to working with the lead agencies. He also noted that NIH leadership has met with the Office of Management and Budget, the White House Office of Science Technology Policy, and the lead agencies to familiarize them with what NIH does and what is most important to NIH's constituents. In addition, the lead agencies will make presentations at the upcoming national meeting of science education grantees, SciEd 2013.

Dr. Anderson reported that the Harvard Medical School announced it will close the New England National Primate Research Center (NEPRC) over the next two years. Harvard cited its strategic plan and financial considerations as the reasons for this action. The NEPRC houses 1,900 monkeys and supports about 130 projects and 150 employees. Harvard will work with the Office of Research Infrastructure Programs (ORIP, DPCPSI), and the other seven national primate research centers to transfer its animals and protect its scientific investment, and help investigators make necessary transitions.

Dr. Anderson closed his presentation by noting the devastation of research infrastructure in the upper Mid-Atlantic and Northeast as a result of Hurricane Sandy. The hurricane relief passed by Congress includes relief funds for restoring research infrastructure at universities affected by the storm. NIH will award an additional $5 million in grants to replace expensive shared instruments that were lost or damaged. A request for applications, totaling $9 million, also has been issued to support the restoration of lost animal colonies, related materials, and equipment. A program that will devote $66 million to restore damaged biomedical research facilities is pending.

Discussion Highlights

- It is not clear why several programs, particularly the Clinical Research Training Program for medical students, were targeted for elimination in the President's budget. Dr. Anderson speculated that several programs were likely eliminated because of their focus on K-12 education.

- The SEPA program sits at an interface between health science education and health literacy. It is important that this focus is not lost, particularly at a time when consumers need to be informed about health decisions.

- The President's proposed budget does not include a budget for the NIH's Office of Science Education.

- The New England National Primate Research Center does not house chimpanzees. The decision to close the Center was not influenced by the Council working group's report on the use of chimpanzees in research.

- Some ORIP-supported resources also have reached out to facilities affected by Hurricane Sandy, particularly animal facilities, to help them re-establish colonies. New York University was hit particularly hard, but the response from NIH, the Federal Emergency Management Agency, and other universities in the area has been a good demonstration of the way communities can pull together.

III. THE NIH COMMON FUND EPIGENOMICS PROGRAM

A. Overview

Dr. John Satterlee of the National Institute on Drug Abuse highlighted components and successes of the NIH Common Fund Epigenomics program, which has supported 68 grants for a total investment of $200 million. The Program encompasses several components and goals:

- The discovery of novel epigenetic marks. Dr. Satterlee noted that when the project began, investigators knew important marks existed, but they did not know what all of these marks were.
- The epigenomics of human health. The Program has supported 33 R01 projects to transform understanding of the epigenomic basis of health and disease. The projects have led to the discovery of altered epigenetic states associated with several diseases/conditions, including Alzheimer's disease, hepatocellular carcinoma, breast cancer, and gestational age at birth.
- Technology development. The Program includes three initiatives to support the development of technologies that will revolutionize epigenomic research. New technologies developed through these projects include a nanofluidic

device to look at single molecules and positron emission tomography imaging agents to look at histone deacetylases.

- Mapping centers, which aim to generate a comprehensive epigenomic map from normal human cells and tissues. So far, 42 human methylome datasets and 79 comprehensive epigenetic datasets have been completed. The data are publicly accessible at http://www.roadmapepigenomics.org.
- Program integration and outreach through yearly investigators' meetings, workshops, and international efforts with partners such as the European Union, Canada, Germany, Japan, Italy, and South Korea.

Dr. Satterlee noted that the Epigenomics Program has resulted in 301 publications as of the week before this meeting. He also noted a workshop held in 2011 to examine how epigenomic discoveries can be translated to improvements in human health. Several Institutes and Centers (ICs) have particular interest in epigenomics, so transition of this program from the Common Fund is not anticipated to be problematic.

B. A Roadmap to the Living Genome

In the genome, DNA is packaged around nucleosomes and folded into chromatin. The nucleosomes are the fundamental units of chromatin, but they are punctuated by free DNA regions that are bound by sequence-specific proteins. These regions include gene promoters, enhancers, and silencers. Site-specific processes, such as transcription initiation, begin with the binding of DNA-binding proteins, which recruit enzymes to modify the chromatin. Dr. John Stamatoyannopoulos of the University of Washington, described efforts to map these epigenetic modifications and events, which can provide clues to pathophysiological processes.

Dr. Stamatoyannopoulos and other investigators supported by the Epigenomics Program have used molecular biology tools to capture DNA sequences associated with epigenetic events and applied next-generation sequencing to map these regions on the genome. To account for the various dynamics of the epigenome among different cell types, they have mapped features to a wide variety of human embryonic stem cells (hESCs), primary hESC derivatives, induced pluripotent stem cells, and primary adult and developing human cells and tissues, focusing exclusively on normal tissue to provide a basis for later studies of disease. Thus the Epigenomics Program has resulted in the generation of approximately 3,000 datasets from more than 400 cellular states, along with 80 highly information-rich "complete" epigenomes that incorporate multiple experimental data types assayed from the same cell/tissue type. These resources are accessible through public genome browsers, and investigators can look more closely at a particular region and see the epigenome for a particular cell or tissue type.

During this work, investigators have identified general biological features that will be important to remember as these data are used in the mapping of human diseases and traits:

- Most epigenomic features are highly cell or lineage selective. The genome is partitioned into specialized compartments at the level of cells, lineages, and tissue groups.
- Gene regulation operates at a distance and is complex. Regulatory DNA regions typically regulate genes located thousand or even hundreds of thousands of base pairs away along the linear genome, although genes and their control elements are brought physically closed in the nucleus through the folding of chromatin.
- The epigenome can "remember" prior cellular states. Changes to regulatory DNA accessibility occur as cells divide and differentiate, and some of these changes appear to persist permanently indicating that epigenome alterations may comprise a type of memory that is inherited from one cell to another.
- All genetic variation is interpreted ultimately in an epigenetic context. Efforts to merge epigenomic maps with data from genome-wide association studies (GWAS) reveal that 95% of the most highly disease- and trait-associated variants are located in the non-coding, regulatory regions of DNA, usually in recognition sites for transcription factors involved in cognate biological processes. In addition, disease-associated variants cluster in regulatory pathways and form regulatory networks. Most of these variations occur in regulatory DNA that first appears in the fetal epigenome, pointing to early developmental contributions to many traits and disease processes.

One paradigm for disease research is the identification of disease-associated genes and pathways that can be manipulated. However, in light of the above features, the information gained from such studies should be corrected to account for the epigenomic circuitry. With these living epigenomic maps, investigators can get a better picture of what occurs with the disease-associated variants they identify. They can examine complex diseases, and they can separate signals coming from each parental allele when analyzing data from heterozygotes. Thus epigenomic analysis can add substantial power and depth to the information obtained through GWAS.

Discussion Highlights

- The Epigenomics Program has been highly collaborative. All data were deposited into the data coordinating center as they were generated and made publicly accessible, and centers exchanged samples. In addition, the Program was able to produce data at an accelerated rate over time because of a highly effective operational structure adopted by the Program.
- The identification and analysis of comprehensive regulatory networks can be a powerful strategy for assessing gene function, and is more general and scalable than one-by-one gene knockout or RNA silencing strategies.

- Living epigenomic maps have the potential to increase the efficiency and efficacy of drug development by pharmaceutical companies. These data can help validate potential drug targets, as well as point to ways to minimize drug toxicities.

- The epigenome maps created to date, although extensive, are only the beginning, as they cover only a fraction of the profound diversity found among human cell types.

IV. REMARKS BY THE NIH DIRECTOR

Dr. Francis Collins noted that NIH is facing a "best of times, worst of times" scenario, where it must operate under enormous budgetary restraint at a time of exciting scientific advances. He reminded the Council that NIH budgets, adjusting for inflation, have remained flat since 2003 and because of the sequester NIH is essentially at the 2001 funding level. As a result, NIH is funding fewer grants—success rates for research project grants are 15% or less—and many scientists are wondering about the future of biomedical research. At the same time, other countries, such as South Korea, China, Singapore, and even Germany are increasing their investments in biomedical science, having observed how such investments have driven the economy in the United States. Dr. Collins acknowledged that the current state of affairs is not sustainable, and he emphasized the need for all in the biomedical research community to make their case for continued investments in this enterprise.

Despite these constraints, Dr. Collins noted several exciting developments. With the decreasing costs for sequencing, the ability to use imaging technologies to follow various processes, access to electronic medical records, and other advances, the research community now has the ability to generate huge amounts of information from various perspectives. The biomedical research community has a responsibility to train investigators in a way that will take advantage of the opportunities afforded by Big Data. In response to a charge from Dr. Collins, the Advisory Committee to the Director (ACD) convened a working group to further explore this issue. In response to the ACD's recommendations, NIH has established new internal governance and oversight bodies; a new trans-NIH initiative, the Big Data to Knowledge (BD2K); and is recruiting for a new position of Associate Director for Data Science.

The ACD convened two other working groups to explore issues facing the biomedical research workforce. They provided their reports in 2012 and NIH has been busy planning to implement their recommendations. One group made recommendations regarding training for Ph.D.s. A second group made recommendations to increase diversity in the biomedical research workforce. In response to the diversity recommendations, NIH will create a new program, Building Infrastructure Leading to Diversity (BUILD), to provide research experiences in institutions that have a larger number of students from underrepresented minority groups and have limited research grant support from

the NIH. NIH also is creating a National Research Mentoring Network, recruiting a Chief Officer for Scientific Workforce Diversity, and developing better ways to track trainees and assess the programs already in place.

Dr. Collins highlighted the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative, which was announced by the President on April 2 of this year. Brain disorders are the nation's largest source of disability, and the rates of and costs associated with these disorders are increasing. As noted by President Obama, the BRAIN initiative will provide investigators with the tools needed to get a dynamic picture of the brain in action. The initiative will include government partners, including the NIH, the National Science Foundation, and the Defense Advanced Research Projects Agency, and private partners such as the Allen Institute for Brain Science, the Howard Hughes Medical Institute, and the Salk Institute for Biological Studies.

The NIH BRAIN initiative will aim to accelerate the development and application of innovative technologies and integrate studies of neuronal and circuit activity to construct a picture of brain function. NIH has convened a team of experts to establish specific goals and timetables. The team will provide at least an outline of goals by the end of this summer and a broad long-term view by the end of the summer of 2014. NIH is organizing a series of workshops, with opportunities for broad input from the scientific community.

Another development is the National Patient-Centered Clinical Research Network (NPCCRN), which will be under the purview of the Patient-Centered Outcomes Research Institute (PCORI). Creation of the Network is motivated by a need to overcome the challenges and expenses associated with conducting major clinical studies in the real world. The NPCCRN is envisioned as a highly representative network of 20-30 million covered individuals who have opted for longitudinal follow-up over many years. It would establish an infrastructure with an efficient biobank, electronic medical records with interoperability across sites, data access policies that provide for broad research use while protecting privacy and confidentiality, and governance with extensive patient participation in decision-making. Such a foundation would enable large trials to be conducted at significantly lower cost. PCORI has issued two funding announcements, described in an article in *Science Translational Medicine*, to create both a clinical data research network, which will include health delivery systems that have access to and can administer consent to a large number of patients with electronic medical records, and a patient-powered research network, which will have resources to link patients with clinical data research networks. Dr. Collins emphasized that the Patient-Centered Clinical Research Network will not replace other clinical research projects. Rather, it will support comparative effectiveness research and outcomes research on practices that are already standard of care.

Dr. Collins closed his remarks by noting that, even in the face of severe budget constraints, NIH remains determined to identify opportunities to accelerate biomedical research. He noted that hunkering down would be the worst thing to

do, whereas new projects can help bolster the case for continued investment in science.

Discussion Highlights

- NIH recognizes the opportunities afforded by research in animal models. While no assurances can be made in light of the budget issues, NIH will continue to support animal research.

- The BRAIN initiative is complementary to the European Human Brain Project, which will build complex sets of circuits *in silico* to model how the brain works. Leadership from both initiatives is communicating. Avenues through which patient advocacy organizations can coordinate with NIH to buffer the cuts and perhaps improve the efficiency of research coordination are being explored. The Foundation for NIH is positioned to broker public-private partnerships.

V. COMMON FUND CONCEPT CLEARANCE AND DISCUSSION

Dr. Elizabeth Wilder, Director of the Office of Strategic Coordination (OSC), DPCPSI, reviewed the Common Fund strategic planning process, which involves a large effort to obtain input from the community and from IC Directors and staff about areas of scientific opportunity and challenges facing the biomedical research community. She pointed out, however, that because of the sequester, the strategic planning meeting for 2015 CF initiatives was canceled. Thus the list of concepts presented to the Council for clearance came from IC Directors and their staff, who are in continuous communication with the scientific community. From the original list of 20 concepts, OSC removed those that were duplicates, were IC-specific, or had been cleared previously, leaving 7 for clearance.

Dr. Wilder reminded the Council that Common Fund programs must be transformative, catalytic, synergistic, and cross-cutting. She also noted that the concepts presented to Council are still at early stages in development and therefore broadly written. Thus, as the Council considered these concepts, they were asked to assess: whether the concept met the criteria for Common Fund programs; if it did not meet the criteria in its present form, whether it could be re-focused to produce a Common Fund program; and where a Common Fund investment in the concept could have the greatest impact.

Normally, Council reviews a larger list of concepts online and votes “yes,” “no,” or “maybe,” with “maybe” votes applying to concepts that show promise but need more development and are brought back to Council. In light of the small number of concepts, for this round of concept clearance, the Council was asked to vote only “yes” or “no.” Concepts receiving “no” votes will undergo no further development. Those receiving “yes” votes will be considered by Drs. Anderson and Collins and potentially developed further by a trans-NIH group of staff and

OSC, who will conduct workshops, prepare requests for information, and other efforts toward community outreach.

In response to questions from the Council, Dr. Wilder noted that because these concepts are in early stages of development, it is difficult to determine what the final initiative will look like and what the cost will be. However, she asked for Council's input in shaping the scope of these concepts. She also noted that decisions about which IC will implement the final program are made essentially through volunteering, when the IC Directors meet to discuss cleared concepts.

The following concepts were considered for FY 2015 programs.

A. Gene Regulatory Networks: A Foundation for Therapeutic Discovery

Computational models of gene regulatory networks could help investigators predict genetic control of cellular functions under normal and abnormal conditions. Such models are now feasible through advances in bioinformatics and in genomic sequencing and analysis. A potential Common Fund program in this area would aim to attain Boolean-level global models for the regulation of embryonic development in zebrafish, *Xenopus*, chick, and mouse models. The program could involve cooperative agreements to bring together investigators and to establish shared data repository and computational modeling coalitions. Each coalition would provide independent investigators with access to facilities, data, and expertise. Such a program could: provide an in-depth understanding of endogenous control mechanisms; facilitate the identification of targets for intervention; provide a framework for the understanding of the effects of variants on disease; and, identify sensitive and specific markers in disease and clinical processes.

Discussion Highlights

- Such a concept should build on the Epigenomics Program.

- Although the four proposed animal models are used commonly for research in developmental biology, focusing on these models alone is too specific. The concept should be broadened and include human participants. This point was a matter of debate, however. Other Council members suggested that the program could choose one model organism, identify gaps, then build further by addressing those gaps in other models.

- The focus on Boolean-level models also is too specific. Investment in the development of statistical models to reconstruct developmental gene-regulatory networks also should be considered.

- The National Human Genome Research Institute and the National Institute of General Medical Sciences have expressed an interest in gene-regulatory

networks, but any proposed efforts are not as large as what is proposed here.

- NIH should consider adding general biomedical questions, such as the mechanisms underlying limb regeneration, as frameworks to work within.

- The proposed program would support the building of coalitions and the provision of resources to investigators, but it is not clear that the program would support actual investigations. However, as the program is developed, it could include demonstration projects.

Vote

A motion to clear the concept was forwarded and seconded. The motion passed (13 votes for, 7 votes against), and the concept was cleared.

B. Sustained-Release Pharmacologic Formulations to Prevent and/or Treat Chronic Diseases

Patients do not adhere to medication regimen for many reasons, including the frequency of administration. The proposed concept would aim to develop sustained-release formulations to improve patient adherence. A potential program could involve initiatives to: identify behavioral factors affecting adherence; identify attributes of sustained-release formulations contributing to acceptability by patients; conduct milestone-driven preclinical and clinical evaluations of new products; develop new formulation technologies and platforms; develop sustained-release forms of existing treatments; and, identify and develop novel drug compounds that are more amenable to sustained-release formulations. Such a program could help to improve patient adherence, resulting in better health.

Discussion Highlights

- Although such a program might be difficult, it might address those diseases where good medications are available but adherence is low.

- A program in this area should be conducted in collaboration with the pharmaceutical industry. In addition, it is not clear how this program would differ from efforts that might be ongoing in the industry, which has an intellectual property incentive for developing sustained-release formulations.

- At present, sustained-release formulations result in larger pills, which might not facilitate improved adherence. In addition, with advances in mobile devices, patients already have some tools to help ensure adherence to their medications. It is not clear this concept would be transformative.

- If the concept moves forward, it should be broadened to be more cross-cutting, for example, by exploring delivery of more than drugs.

Vote

A motion to clear the concept was forwarded and seconded. The motion failed (2 votes for, 18 against), and the concept was not cleared.

C. Cachexia-Defining Measures, Triggers, and Metabolic Reprogramming to Develop Early Interventions

Cachexia is a wasting syndrome involving the loss of muscle with or without the loss of fat mass. It is characterized by unintended weight loss and accompanies many diseases. The mechanisms and triggers of cachexia are not understood, and the current strategy of providing calories does not adequately address it. A program focused on cachexia would aim to provide an in-depth understanding of mechanisms underlying cachexia and its progression and ultimately, to inform the development of new treatments. Initiatives would include: observational studies on the physiology and molecular course of cachexia; collaborative programs between basic and clinical scientists; the development of model systems; the application of 'omic technology to identify altered transcriptional and metabolic programs, biomarkers, and susceptible populations; and, the development of functional and physical measures of early cachexia. Such a program could facilitate the development of diagnostic and therapeutic measures and provide pathways for new drug development, and translation of findings to clinical practice could improve outcomes for a variety of diseases.

Discussion Highlights

- This concept could be broadened to explore metabolic disease in general, as weight regulation is a major medical issue. A systems biology approach could be incorporated. This was a point of debate. Some Council members preferred to keep the focus on cachexia alone, while others suggested sarcopenia, defined as muscle wasting, could be added without broadening the concept too widely.

- It is not clear whether there is a standard of consensus definition of cachexia. Such a definition is needed to inform the development of good models, the identification of biomarkers, and the study of the natural history underlying cachexia.

- The program could tap into 1980s work on cachectin, also known as tumor necrosis factor alpha. However, this should not be the only focus of the program.

- NIH should consider a tiered approach, with the first stage aiming to better define cachexia and an opportunity for the program to gear back if early observational studies and molecular analyses rule out the cross-cutting nature of cachexia.

Vote

A motion to clear the concept was forwarded and seconded. The motion passed unanimously, and the concept was cleared.

D. Affordable Technologies for Global Health Through Existing Biomedical Networks

Across the globe there continue to be disparities in access to health technologies. The proposed program would aim to develop technologies to improve care for individuals in under-resourced environments. It would support: the development of low-cost technologies for evaluation, diagnosis, and treatment; the development and implementation of technology that is easily transported, maintained, and operated; the formation of consortia; collaboration between developers and health practitioners; and translation of reduced-cost technologies to the United States.

Discussion Highlights

- The definition of technology should be expanded to include more than devices. For example, mobile apps, vaccines, or drugs also might be developed. The proposal for a data repository should be expanded to include a repository and the informatics and tools needed to analyze data.

- Although it is tempting to focus on low cost, the program would do better to focus on value and impact, or cost-effectiveness. Focusing only on low cost will prevent the health care community from determining how to use the best technologies in a sustainable way.

- It is highly unlikely that low-cost technologies would be developed within the United States; it is much cheaper to develop such technologies globally and transfer them back.

- The program should promote bidirectional learning, rather than promote the perception that “we know best.” Investigators and developers supported by the program should take opportunities to learn from successful practices elsewhere.

- The concept likely will leverage existing IC-funded networks conducting biomedical research in under-resourced countries, rather than starting from scratch.

- NIH should consider leveraging resources with philanthropic organizations, such as the Gates Foundation, which also are interested in global health. Other potential partners include the pharmaceutical industry and the small business community.

Vote

A motion to clear the concept was forwarded and seconded. The motion passed (11 for, 9 against), and the concept was cleared.

E. Human Cell Identity and Lineage Project

Knowledge of the human cellular space is not keeping pace with the growing knowledge about other areas of biology. The proposed concept, which would be related to that for gene-regulatory networks, would aim to develop a cell identity and lineage map of human development by providing a set of verifiable definitions of human cell types and mapping their relationships. This is related to the concept for gene-regulatory networks. In addition to definitions and lineage maps for each cell type, the concept also would: involve new technologies for imaging, lineage tracing, cell isolation, and functional assessment; establish human cell standards, reference resources, and repositories; develop a widely accessible database; and, conduct studies on ethical, legal, cultural, and social implications. Such a program could benefit the entire clinical and research enterprise from the bench and bedside, and it could particularly aid research on rare diseases.

Discussion Highlights

- NIH should take care not to treat cell lineage and behavior as a static process. The final program should account for differences in cell behavior, depending on their culture conditions, and for cell differentiation as well as cell type. For example, a macrophage can differentiate into various states based on its environment.

- The proposed concept might be a naïve approach to this problem; it needs to keep pace with what is known about human cells to avoid focusing on those types that are not biologically significant. For example, definitions of cell types are changing constantly.

- It might be better to support pilot projects to determine whether such a concept is doable.

Vote

A motion to clear the concept was forwarded and seconded. The motion failed (9 for, 11 against), and the concept was not cleared.

F. Proteostasis (Protein Homeostasis) Project

The disruption of protein homeostasis has been implicated in many diseases, but the underlying etiology is not understood. The proposed concept would aim to survey proteostasis function both in health and in multiple classes of disease to determine how protein imbalance contributes to disease and to aid the development of novel therapeutics. Initiatives would include: a systematic assessment of proteostasis in normal development, aging, and disease; development of new technologies and a central bioinformatics resource; addressing how non-cell-autonomous stress can induce disease; addressing how environmentally induced changes in protein conformation cause heritable disease through protein-based epigenetics; high-throughput screens to identify novel modulators of proteostasis; and clinical trials with such modulators.

Discussion Highlights

- This is a cross-cutting issue, as many diseases involve protein misfolding and stress of the endoplasmic reticulum (ER).

- This concept appears to be too broad, and efforts to understand protein homeostasis, ER function, and autophagy are already ongoing. It is not clear how the proposed concept would be transformative.

- NIH should consider directing a potential program toward understanding the impact of treatment options, rather than on basic mechanistic studies.

Vote

A motion to clear the concept was forwarded and seconded. The motion passed (19 for, 1 against), and the concept was cleared.

G. 3D Nucleome

It is not clear how changes to the genome and epigenome affect the three-dimensional (3D) architecture of the cell nucleus and thus affect the tightly controlled transcriptional equilibrium. The proposed concept would aim to generate comprehensive 3D maps of the interphase nucleus, explore how the cell transcriptome is affected by changes to the 3D structure, explore the functional role of epigenetic modifications and chromatin remodeling, and uncover mechanisms governing lineage-specific nuclear conformations and their perturbation in disease states. Initiatives would include: consortia to address methodological and conceptual aspects of the 3D nucleome; work in an international environment; a reference database and novel experimental, analytical, and bioinformatics; and, scientific meetings. Such a program would add another level of understanding in the area of gene regulation and provide new information about structure-function relationships, the complexity of

multicellular organisms, and changes induced by genomic and epigenomic changes.

Discussion Highlights

- This concept meets all criteria for a Common Fund program, but it could be broadened to allow several approaches to be used.

- Despite advances in epigenomics, the field remains limited by the lack of understanding of how DNA is packed into the nucleus and how the nucleome is organized. This project could complement the Epigenomics Program.

Vote

A motion to clear the concept was forwarded and seconded. The motion passed unanimously, and the concept was cleared.

Final Statements

- Concepts cleared today will be discussed by NIH leadership, who will select ones to move forward. Updates on those selected for further development will presented to the Council at the January 31, 2014 meeting.

- Although programs can remain in the Common Fund for 10 years, DPCPSI aims to demonstrate impact in a shorter amount of time.

VI. ORIP CONCEPT CLEARANCE: MUTANT MOUSE REGIONAL RESOURCE AND INFORMATICS CENTERS

Dr. Oleg Mirochnitchenko of the Division of Comparative Medicine, ORIP, DPCPSI, reviewed the Mutant Mouse Regional Resource and Informatics Centers program (MMRRC), which was discussed at the January 2013 Council meeting. Initiated by the National Center for Research Resources in 1999 and transferred to DPCPSI in 2012, the program currently includes four centers at the University of Maine, the University of North Carolina at Chapel Hill, the University of California, Davis, and the University of Missouri plus a data coordinating center at the University of California, Davis. The External Advisory Committee recommended the name of the program be changed to "Mutant Mouse Resource and Research Centers" in recognition of MMRRC's leadership in the archiving and distribution of mouse strains and the growing importance of the innovative research projects at the centers.

Awards will continue to support and advance the MMRRCs, thus facilitating research by qualified biomedical investigators, as well as high-risk, high-reward research projects that complement the needs of the MMRRC Research Consortium. ORIP proposes the publication of a request for applications supporting a U42 Cooperative Agreement funding mechanism. This will be a

competition limited to the existing Centers. ORIP anticipates four competing continuation awards, contingent on the availability of funds, with an estimated direct cost of $900,000 to $1 million per award, for a period of 5 years.

Discussion Highlights

- ORIP plans for this to be a limited competition to continue the substantial investments and the infrastructure already in place at these centers. In the past, when an existing center was found not to meet criteria for renewal, NCRR issued parallel requests for applications: one for existing centers, and one for a new center.

Vote

A motion to approve the concept was forwarded and seconded. The motion passed unanimously. As a principal investigator at an MMRRC, Dr. K.C. Kent Lloyd recused himself and left the room during the discussion and vote.

VII. REVIEW OF GRANT APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[1] Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Council would represent a real or perceived conflict of interest. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect. The *en bloc* vote for concurrence with the initial review recommendations was affirmed by all Council members present. During the closed session, the Council concurred with the review of 231 Common Fund (Transformative Research Awards) with first year, direct costs requested of $153,968,176, and 55 ORIP applications with first year, direct costs requested of $17,903,719.

VIII. VOTE ON COUNCIL OPERATING PROCEDURES

Dr. Anderson presented a revised draft of the Council Operating Procedures. This draft incorporates edits made by the Council at the September 2012 meeting and during subsequent email discussions.

Section I. The revised draft clarifies that the Council ***advises*** on policy, rather than develops it.

Section II. The revised draft: adds an example of how the Council can change the order in which applications are considered; provides examples of reasons the

[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.

Council can recommend that an application not be funded; clarified when individual grant applications can be provided to the Council members upon request; clarified the process for appeals; corrected statements about en bloc voting; and clarified aspects of ORIP application review.

Section III. The draft has been updated to reflect current procedures for Common Fund concept clearance and to clarify the procedure for ORIP concept clearance. The section also clarifies authorities delegated to DPCPSI staff by the Council.

Discussion Highlights

- Foreign applications for institutions subcontracting with a U.S. institution might not be subjected automatically to an additional review by the Council.

- Council members receive summary statements, but not grant applications for their second level reviews. However, they may request the entire application if it will aid their review with a strong justification.

- The Council suggests revising the procedures to allow flexibility in the concept clearance process for Common Fund programs. A mechanism to allow the Council to discuss concepts at a face-to-face meeting if the number of concepts is small will be added to the procedures.

Vote

A motion to approve the Council Operating Procedures, with the addition of a process mechanism added for Common Fund concept clearance, was forwarded and seconded. The motion passed unanimously.

IX. EVALUATION OF NIH DIRECTOR'S PIONEER AWARD

Dr. Anderson presented highlights of the evaluation of the NIH Director's Pioneer Award Program. He noted that one of the first programs in the NIH Roadmap/Common Fund, the NIH Director's Pioneer Award Program, was established in 2004 to address concerns that existing mechanisms did not promote innovation and risk-taking. The program targets creative investigators, at all career stages, who propose paradigm-shifting research with high-risk designs. Applicants must submit a five-page essay and three reference letters. No preliminary data or budget estimates are required, but the proposed work must represent a substantial departure from the applicant's area of interest.

The Pioneer Award program has been touted by members of Congress and the scientific community as an example of successful government investment in innovation. However, R01 investigators also have conducted spectacular, paradigm-shifting research. To address whether the Pioneer Award (DP1) mechanism has been better at identifying and supporting innovative, high-impact research, NIH commissioned the Institute for Defense Analysis-Science and Technology Policy Institute to conduct a formal, comparative evaluation. The

Institute compared Pioneer awardees with: Howard Hughes Medical Institute (HHMI) awardees, who are selected based on innovation and past performance; a group of "matched R01s," or investigators with similar characteristics to those receiving Pioneer awards; a group of random R01 awards with similar budgets to the Pioneer awards; and Pioneer finalists who were not funded. The evaluation consisted of a bibliometric analysis of more than 20,000 publications, as well as a blinded review by 94 experts of impact and innovativeness.

Compared with matched R01s, Pioneer awardees produced more publications per grants, but the same number per dollar spent, and their publications have a higher impact factor. A publication "tail" also was seen among Pioneer awardees. Expert review indicated that impact and innovation are higher among Pioneer awardees. The comparison with HHMI awardees indicated that although the total number of publications and citations is higher among HHMI awardees, the number of publications and citations per dollar invested is the same. Pioneer awardees appear to publish in lower-impact journals than their HHMI counterparts. However, expert review suggests that the level of impact and innovation is the same between the two groups. Compared with random R01 awardees, the number of citations per dollar and publication, along with journal impact factor, appears to be higher among Pioneer awardees.

Higher funding levels thus appear to result in a higher portfolio-level impact. The differences seen between Pioneer awardees and matched R01s might arise from differences in funding levels of program characteristics, and the differences between Pioneer awardees and random R01s might arise from differences in investigator characteristics, program characteristics, and research areas. Differences between the Pioneer awardees and HHMI awardees most likely does not arrive from differences in flexibility or risk-taking, but from differences in funding level and stability, investigator characteristics, and areas of science.

Dr. Anderson noted that this was the second comparative review of outcomes ever done; most evaluations tend to be anecdotal. He also pointed out that the data compel NIH to continue supporting this program to celebrate trail-blazing opportunities. However, scientific progress arises from several pathways and funding mechanisms, and R01-supported research provides the depth and breadth needed to afford meaningful and directed understanding.

A full report of this evaluation is available on the Common Fund website.

Discussion Highlights

- The findings of this evaluation show that NIH is receiving what it intended for its investment.

- The matched R01 group comprised investigators from similar institutes, career stage, or area of science.

- The comparison to matched R01s needs more detail, for example by taking several samples of applications. Results of this comparison could encourage ICs to devote a proportion of their portfolios to investigator-focused awards, rather than project-focused ones.

- There might be some bias against Pioneer awardees. Because these awards represent new directions, it might take a while for investigators to get up and running. It is likely that Pioneer awardees will have even more publications in the longer term.

- Whether investigators who completed a Pioneer award went on to compete successfully for a new grant has not been explored. To sustain momentum among Pioneer awardees, NIH could consider a pathway from the Pioneer grant to the first 5 years of R01 funding at a similar level. Although Pioneer awardees appear to be ahead, NIH study sections for R01 grants are still inherently conservative, and a pool of grants based on performance, and not on what study sections think are the best metrics, is needed.

X. OFFICE OF DISEASE PREVENTION

Dr. David Murray, Associate Director for Prevention, NIH, and Director of the Office of Disease Prevention (ODP), reviewed the Office's history and future directions. The Office aims to improve health by increasing the scope, quality, dissemination, and impact of NIH-supported prevention research in collaboration with ICs and other partners. ODP casts a wide net by broadly defining prevention to include health promotion, prevention of disease-onset, and prevention of disease progression. ODP also promotes research in a wide variety of disciplines.

ODP was created in 1986 following passage of the Health Research Extension Act. The Prevention Research Coordinating Committee and Consensus Development program moved to the Office at this time, followed by the Office of Dietary Supplements in 1994 and the establishment of the Robert S. Gordon lectures in 1995. The Office developed the Medicine in Media program in 2003 to help journalists and editors evaluate and report on medical research, and it established the Medicine: Mind the Gap seminar series in 2007 to explore areas in which conventional wisdom might be contradicted by recent evidence. The Evidence-Based Methodology Workshops were established in 2012 to identify methodological and scientific weaknesses and to move prevention research forward. The Tobacco Regulatory Science Program, a trans-NIH collaboration with the U.S. Food and Drug Administration's (FDA) Center for Tobacco Products (CTP), was moved to ODP in 2012. This collaboration funds research to support the regulatory authority granted to FDA by the Family Smoking Prevention and Tobacco Control Act of 2009.

The Office continues to run these programs, co-fund research projects and meetings, and collaborate with partners on initiatives such as HealthyPeople 2020, the National Prevention Strategy, and the U.S. Preventive Services Task Force.

The bulk of current and planned funding opportunities for FY 2013 focus on the Tobacco Regulatory Science Program, with R and K awards, P50-supported Tobacco Centers of Regulatory Science, and competing revisions of P30 awards encompassing 10 areas of research related to tobacco use.

ODP is also developing its first strategic plan. A working group has been established and focus groups conducted with program and review staff across NIH, and Dr. Murray has met with IC Directors to obtain their input. The draft strategic priorities for the next 5 years are to:

- Systematically monitor NIH investments in prevention research.
- Identify and promote prevention research areas deserving of expanded effort and investment.
- Improve the quality of methods in prevention research.
- Encourage the development of collaborative research projects.
- Identify and promote the use of effective interventions.
- Increase the visibility of prevention research at NIH.

Dr. Murray closed by sharing his vision that ODP will be seen more widely as a valuable resource to NIH and the broader research community by 2018.

Discussion Highlights

- ODP interacts regularly with the Centers for Disease Control and Prevention (CDC) and is actively involving CDC in its portfolio analysis. However, the Office aims to interact more closely with CDC so that NIH can be more responsive to CDC reports and provide input to the Community Guide and statements by the U.S. Preventive Services Task Force.

- The research supported by NIH through the Tobacco Regulatory Science Program generates data that can be used by the FDA in making its regulatory decisions. NIH does not inform policy directly. Although there has been no pushback from the tobacco industry, the industry does follow this work closely. NIH conducts this work carefully.

- Research efforts in school-based prevention programs can be successful when they align with the educational activities of the school.

- Almost every IC supports prevention research, although the level of support varies considerably.

XI. CLOSING REMARKS

Dr. Anderson thanked Council members and speakers for their contributions at this meeting. The next Council meeting will be held on September 24, 2013.

XII. ADJOURNMENT

Dr. Anderson adjourned the meeting at 4:35 p.m. on May 14, 2013.

XIII. CERTIFICATION

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

James M. Anderson, M.D., Ph.D.
Chair, NIH Council of Councils
Director, Division of Program Coordination,
Planning, and Strategic Initiatives (DPCPSI)
Office of the Director (OD)
National Institutes of Health

7-2-13
Date

Robin I. Kawazoe
Executive Secretary, NIH Council of Councils
Deputy Director, DPCPSI
OD, NIH

7/2/2013
Date