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
June 5, 2012

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 (CoC). The meeting opened at 8:30 a.m. on Tuesday, June 5, 2012, in Building 31, 6th Floor, Room 10, on the NIH Campus, Bethesda, Maryland.

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
STEPHEN L. BARNES, PH.D., University of Alabama at Birmingham
F. XAVIER CASTELLANOS, M.D., New York University School of Medicine, New York, NY
DAVID W. CRABB, M.D., Indiana University School of Medicine, Indianapolis, IN
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
DANIEL H. GESCHWIND, M.D., PH.D., David Geffen School of Medicine, University of California, Los Angeles
MAE O. GORDON, PH.D., Washington University School of Medicine, St. Louis, MO
RICHARD M. GREENWALD, PH.D., Simbex, iWalk, Thayer School of Engineering, Lebanon, NH
PETER J. HOTEZ, M.D., PH.D., Baylor College of Medicine, Houston, TX
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
H. KIM LYERLY, M.D., Duke University Medical Center, Durham, NC
JEAN MCSWEENEY, PH.D., R.N., F.A.H.A., F.A.A.N., University of Arkansas for Medical Sciences, Little Rock, AR
JOYCE A. MITCHELL, PH.D., University of Utah, Salt Lake City, UT

REGIS J. O'KEEFE, M.D., PH.D., University of Rochester School of Medicine and Dentistry, Rochester, NY
REGINA RABINOVICH, M.D., Bill & Melinda Gates Foundation, Seattle, WA
DAVID L. VALLE, M.D.,[1] Johns Hopkins University School of Medicine, Baltimore, MD
JOHN W. WALSH, Alpha-1 Foundation, Miami, FL
GARY L. WESTBROOK, M.D., Oregon Health and Science University, Portland, Oregon
TERRIE FOX WETLE, PH.D., Brown University Medical School, Providence, RI
LUTHER S. WILLIAMS, PH.D., Tuskegee University, Tuskegee, AL

2) Liaisons

JANINE A. CLAYTON, M.D., Acting Director, Office of Research on Women's Health, DPCPSI, OD
PAUL M. COATES, PH.D., Acting Director, Office of Disease Prevention, DPCPSI, OD
ROBERT M. KAPLAN, PH.D., Director, Office of Behavioral and Social Sciences Research, DPCPSI, OD
LOUISE E. RAMM, PH.D., Director, Office of Research Infrastructure Programs, DPCPSI, OD
JACK WHITESCARVER, PH.D., Director, Office of AIDS Research, DPCPSI, OD
ELIZABETH L. WILDER, PH.D., Director, Office of Strategic Coordination, DPCPSI, OD

3) Presenters in Attendance

MICHAEL C. CHANG, PH.D., Division of Comparative Medicine, Office of Research Infrastructure Programs, DPCPSI, OD
FRANCIS S. COLLINS, M.D., PH.D., Director, NIH
FRANZISKA B. GRIEDER, D.V.M., Ph.D., Director, Division of Comparative Medicine, Office of Research Infrastructure Programs, DPCPSI, OD
JOHN D. HARDING, PH.D., Division of Comparative Medicine, Office of Research Infrastructure Programs, DPCPSI, OD
ELISABETH KOSS, PH.D., Health Scientist Administrator, Division of Construction and Instruments, Office of Research Infrastructure Programs, DPCPSI, OD
RANDALL S. PRATHER, PH.D., Director, National Swine Resource and Research Center, University of Missouri
RONALD VEAZEY, D.V.M., PH.D., Professor of Pathology and Chair, Division of Comparative Pathology, Tulane National Primate Research Center, Tulane University

4) NIH Staff and Guests

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

[1] Dr. Valle joined the meeting by teleconference and was present from the presentation on the National Primate Research Centers through the Update on Working Group on Chimpanzees in NIH-Supported Research. .

B. Meeting Procedures

Ms. Robin Kawazoe reviewed the following:

- Council members are considered Federal employees during Council meetings and are therefore subject to the rules governing Federal employees.
- Each Council participant has completed and submitted a financial disclosure form and conflict of interest statement as a Federal requirement for membership on individual Institute or Center (IC) advisory councils. Financial disclosures are used to assess real and perceived conflicts of interests, and Council members must recuse themselves from 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 on the DPCPSI Web site and in the *Federal Register*.
- CoC 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 CoC meeting will be held September 5, 2012. CoC meetings in 2013 will be held on January 22, May 14, and September 24.

II. DPCPSI UPDATE

Dr. Anderson reminded the Council about the history of DPCPSI—its legislative creation by the NIH Reform Act of 2006, its operational establishment in 2008, and its purpose in establishing ways to work in a trans-NIH arena and facilitating coordination across the Institutes and Centers on specific themes in research. Dr. Anderson also noted the reorganization resulting from the establishment of the National Center for Advancing Translational Sciences (NCATS) and the dissolution of the National Center for Research Resources (NCRR), and he provided an update on DPCPSI activities.

Two staff offices were created – the Office of Program Evaluation and Performance that focuses on evaluation and required reporting to HHS and Congress on NIH program performance, and the Office of Portfolio Analysis (OPA). OPA is focused on the science of portfolio analysis, including assisting the ICs in identifying and validating the best tools for obtaining useful data and answering their questions. The Office is also establishing a trans-NIH working group to assess the various tools developed by different ICs and share the best practices among all ICs. In addition to helping all NIH ICs improve their portfolio analysis efforts, OPA also engages in portfolio analysis to refine

Common Fund projects. Dr. Anderson noted that Dr. George Santangelo, the OPA Director, will discuss Office activities in more detail at the September Council meeting.

The Office of Research Infrastructure Programs (ORIP), which supports instruments, resources, construction, animal model resources, and coordinates science education activities, is enhancing outreach efforts to identify the scientific community's needs and to make additional investments in animal models. For example, in May 2012 the Division of Comparative Medicine (DCM) held a symposium to review model systems, identify needs for animal models, and discuss how to translate findings from animal models to human research studies in regenerative medicine. Dr. James Thomson, a pioneer in the derivation of human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPS), served as keynote speaker at the symposium, which included participants from 18 ICs and other Federal agencies. DCM is also planning a workshop that will bring together thought leaders in advanced animal models, primarily mice, to discuss next-generation models targeting personalized disease phenotypes and to identify areas for funding. Both meetings are expected to lead to future funding opportunities.

The Office of Behavioral and Social Sciences Research (OBSSR) has recently issued funding opportunity announcements (FOAs) for research on practical interventions to improve medication adherence in primary care, behavioral interventions to address multiple chronic health conditions in primary care, and systems science and health in the behavioral and social sciences. OBSSR has also held or planned several meetings and activities focused on training.

The Office of Strategic Coordination (OSC) is starting three new programs. The first will involve several funding initiatives supporting training, resource development, and technology and standards development to enable metabolomics analyses. Another program, the Genotype-Tissue Expression project (GTEx), builds on a pilot program that aims to link gene sequences to tissue-specific transcript levels. The pilot program has resulted in a national collection system to recover samples from postmortem donors, and the RNA extracted from these samples is of good quality. As a full-scale project, GTEx will aim to obtain samples from 900 postmortem donors, and OSC hopes to add an epigenomics component. The third program involves a set of FOAs to support research using single-cell analysis, as well as the development of technologies and tools to enhance such analysis.

Work by investigators at Yale University, with support from the Office of Research on Women's Health, has found sex and gender differences in the roots of addicts' cravings. These results were published recently in the *American Journal of Psychiatry*. ORWH staff have also given testimony to the National Academies of Science on women of color in the biomedical research workforce, and the Office has taken a lead role in coordinating the Vice President's International Violence Against Women Working Group. A search for a new ORWH Director is ongoing.

The Office of Disease Prevention (ODP) will be gaining new responsibilities in tobacco research coordination as a result of the Family Smoking Prevention and Tobacco Control Act of 2009, which provides additional funding to the U.S. Food and Drug

Administration (FDA) to regulate several aspects of tobacco use. FDA is collaborating with NIH on research related to tobacco regulation, and ODP will coordinate this research and collaboration. A search for a new ODP Director is also ongoing.

Dr. Anderson closed his presentation by introducing the concept of Special Council Review (see below).

Discussion Highlights

- DPCPSI performs portfolio analysis on potential Common Fund concepts once the list of concepts has been narrowed down and CoC has cleared the concepts.

- Although portfolio analysis tools can be powerful and useful, care should be taken in the interpretations of these analyses and the decisions that are based on them. For example, making funding decisions based solely on years of life lost from a disease or condition would have a negative impact on research related to Alzheimer's disease or on rare and neglected diseases.

- ODP is working with FDA to define more clearly the research areas related to tobacco regulation. More information about this collaboration will be presented at the September Council meeting.

III. SPECIAL COUNCIL REVIEW

In response to ongoing economic constraints, NIH developed a policy for Special Council Review for investigators with more than $1.5 million of support in total annual costs. In a pilot project, the Advisory Council for each IC will engage in additional scrutiny of applications from these investigators and apply specific criteria in determining whether these applications should be approved for funding. P01s, multi-component research project grants, and applications with multiple principal investigators are excluded from Special Council Review unless all investigators meet the $1.5 million threshold. Requests for applications (RFAs) are also excluded.

The Council of Councils will use Special Council Review procedures only for ORIP/DCM applications because this is the only DPCPSI Division that supports research project grants (not submitted in response to RFAs). Like other Councils, the Council of Councils will receive a list of the principal investigator's active grants, including end dates and budget; a written summary by the program officer on the thematic differences and potential innovation of the proposed work; and information about the field of research, public health and program priority, and degree to which restricting funding could stifle collaboration. The Council will be asked to review the list of competing awards and the justification and recommendations from ORIP/DCM staff and consider the merit of the application, the DCM mission, the Division's program priorities, the Division's portfolio balance, and the availability of funds. After reviewing these materials and addressing these considerations, the Council will decide whether it concurs with staff recommendations.

The pilot is taking place during the May/June Council meetings, and IC Councils will provide feedback to NIH. NIH will use this feedback as it develops a uniform review policy. IC-specific variations might be developed in consultation with individual Councils.

Discussion Highlights

Council members expressed concern that this policy will place investigators at institutions with high indirect cost rates at a significant disadvantage. In response to these concerns and to questions from the Council, Drs. Anderson and Grieder noted that this policy does not constitute a cap on funding, and it does not mean that investigators with existing total annual costs of $1.5 million will not receive new funding. Rather, the $1.5 million threshold is a trigger for additional scrutiny of new applications from the investigator and for a discussion of the best use of NIH funds. Dr. Anderson also pointed out that training grants (T mechanism) are excluded and that funding from other agencies does not count toward the investigator's $1.5 million threshold for NIH Special Council Review by the Council of Councils.

IV. COMPARATIVE MEDICINE RESEARCH RESOURCES

Dr. Michael Chang introduced DCM by noting that the Division helps to meet biomedical researchers' needs for high-quality, disease-free animals and specialized animal facilities. Through grants and contracts, DCM supports researchers and resources that create, develop, and supply animal models and biological materials, as well as training and career development.

Resource centers form the area of greatest investment, consuming approximately two-thirds of the Division's portfolio. Funding for these resources is determined by the demonstrated need for the resource in the research community; the ability of that resource to serve investigators in a wide variety of research areas; the potential availability of that resource on a local, regional, and national basis; and the inclusion of a research component to generate new, relevant information. Many resource centers have external advisory boards and/or steering committees to advise them on the management of resources. The centers confirm the strains they have by genotyping, and they cryopreserve germplasm, sperm, eggs, and embryos for these strains. They offer a robust health program including husbandry, health consultation, and pathology services, and they provide training, particularly for institutions with veterinary schools that have T32 or T35 training grants.

DCM-supported animal resource centers include:

- Aquatic model resources such as the Zebrafish Resource Center, which contains more than 1,200 lines and distributes approximately 110,000 fish to more than 700 academic institutions and pharmaceutical laboratories per year.

- Invertebrate animal resources such as the *Caenorhabditis elegans* (*C.* elegans) and Drosophila stock centers. The *C. elegans* center is a collection of more than 13,000

genetically defined strains and distributes more than 25,000 worms to more than 3,000 laboratories annually.

- National Primate Research Centers (NPRCs) and other non-human primate resources, including pathogen-free baboon and rhesus macaque colonies.
- Rodent resources such as the Mutant Mouse Resource Centers.
- Other comparative model resources such as the National Swine Resource and Research Centers (NSRRCs).

Discussion Highlights

- DCM supports an aging primate colony, and several of its centers are co-funded by the National Institute on Aging.

V. THE NATIONAL SWINE RESOURCE AND RESEARCH CENTERS (NSRRCs) AND GENETIC ENGINEERING OF SWINE

Across many diseases and ICs, swine have been used extensively as biomedical models of human health. Pig models present some challenges; they are not as readily available as mice, their gestation time is 4 months, and they reach puberty in 7 to 9 months. However, in some aspects they are preferable to rodent models. Swine models are more likely than rodents to have physiologic processes and phenotypes that are similar to those in humans, swine models are more amenable to blood flow measurements and genomic or proteomic methods, and the pig genome is three times closer than the mouse genome in similarity to the human genome.

Dr. Randall Prather, Director of the NSRRC at the University of Missouri, described the NSRRC's overall and highlighted models created or housed at his institution. NSRRC imports pigs, raise them in isolated environments, and distribute models across the United States and Canada. Some naturally occurring models, such as the Ossabaw Island model of type 2 diabetes or the ApoB-hypercholesterolemic pig model, are useful. However, the NSRRC also create new models, often through genetic modification. The NSRRC has an advisory board, advertises its services, and conducts workshops and training, as well as health monitoring.

The genetically modified models housed in the NSRRC at the University of Missouri have been created primarily through somatic cell transfer, either at this site or elsewhere. Many of these models carry modifications useful for medicine or for production agriculture. These models include:

- Models in which genes have been modified or deleted, such that organs from these pigs do not elicit hyperacute rejection or other adverse reactions when transplanted to humans. The University of Missouri is using a two-phase integration system that allows multiple insertions and integrations at the same locus to potentially stack gene

modifications. This technique allows the NSRRC to overcome challenges and limitations associated with Mendelian inheritance.

- Model of retinitis pigmentosa in an NIH miniature pig. These pigs exhibit eye abnormalities similar to those seen in humans with the disease.

- Models in which all or part of the cystic fibrosis gene has been deleted. These pigs exhibit phenotypes, such as lung and gastrointestinal abnormalities and smaller stature, that are seen in humans with cystic fibrosis. The use of swine models has led to the discovery that insulin like growth factor 1 levels are lower in pigs and humans with cystic fibrosis and that bacterial infection precedes the inflammation seen in these patients.

- Models in which genetic modification decreases breakdown and increases bioavailability of human coagulation factors in the pig mammary gland. A herd of 50 to 60 animals could supply the world's needs for coagulation factors.

- Models with genetic modifications that generate cell-tracking tools such as green fluorescent protein tags, which have allowed researchers to study rod and cone progenitors in the eye.

- Models of muscular dystrophy, diabetes, spinal muscular atrophy, and cancer.

Other genetically modified models are under development, both at the University of Missouri and elsewhere.

Discussion Highlights

- If an investigator provides the NSRRC at the University of Missouri with cells, the Center can perform the nuclear and embryo transfers needed to create the model at an approximate total cost of about $24,000. Information on the comparability of these costs to those of rodent models was not available at the time of this presentation.

- The swine model has been used in virology, particularly for pulmonary infections. It is not clear whether other viral infections, such as hepatitis C, have been successfully modeled.

- Post-translational processing in the cystic fibrosis models is similar to that in humans, but researchers there have not yet explored environmental factors, such as diet, that might exacerbate disease. This work, conducted in Dr. Prather's laboratory at the University of Missouri, was funded by the University of Iowa.

- Pigs continue to grow throughout their lives and can reach 2,000 pounds. The University of Missouri NSRRC is transitioning some of its models to NIH miniature pigs to accommodate researchers who want to use swine models but do not have the facilities to house the larger animals.

- A swine model of Alzheimer's disease has been developed in Europe.

- In addition to creating some of its models in mini-pigs, the University of Missouri NSRRC is also advertising and minimizing costs to encourage utilization of its models. The Center will also distribute tissue samples if investigators have no place to house the pigs. Demand has increased dramatically over time.

- The NSRRC Steering Committee meets bimonthly to help the Center prioritize requests.

- Stem cell lines are needed to facilitate genetic modifications. The NSRRC is working on iPS methods, but attempts with hESCs have not been successful.

- For applications such as production of coagulation factors, the pig is preferable to the cow because it performs the post-translational modifications seen in humans and because pigs produce more offspring.

VI. REMARKS BY THE NIH DIRECTOR

Dr. Francis S. Collins focused his remarks on NIH investments in terms of technology, translation, talent, and taxpayer return. He noted that in this time of budgetary pressure, highlighting the return on investment in NIH is important along with highlighting how NIH research improves the health of the nation. Dr. Collins was confident that NIH can make a good case in both areas. NIH has had a large impact on human health in the United States. Over the past 40 years, deaths from heart disease, stroke, cancer, AIDS, and other diseases have decreased. Deaths from cardiovascular disease have fallen by 60 percent over the last 50 years, and with advances in HIV therapies, adults infected in their twenties are now living to age 70 and older. All of these increases in life expectancy translate to a savings of about $3.2 trillion a year.

Technological innovation and advances in biomedical research is one driver of these gains. One obvious example of this comprises advances in DNA sequencing. Over the past 10 years, the cost of sequencing a complete human genome has decreased dramatically, about 12,000-fold, and two companies are expecting to soon be able to sequence an entire genome in 24 hours. These changes have accelerated the discovery of diseases with a known molecular basis, and they will facilitate advances in medical applications and personalized medicine, with dramatic outcomes. An example can be found in the case of fraternal twins who as young children exhibited severe neurological symptoms that were difficult to diagnose. These symptoms worsened as the twins grew older, and a variety of therapies provided only a small benefit. A complete sequence analysis of the twins' genome uncovered an actionable mutation in a neurotransmitter pathway. The twins were started on an appropriate therapy and within days showed considerable improvement. One of them is now competing in track events.

Although advances in sequencing technology have led to the discovery of 4,600 diseases with a known molecular basis, only 250 of them have known therapeutics. Thus translation of discovery into treatment remains an important aspect of NIH's mission.

Molecular discoveries suggest targets for small molecules or drugs, but finding the right molecule takes a long time, and failure is highly likely. The development of new therapies and the productivity per billion spent on research and development have declined despite the dramatic increases in discovery. This frustration has led NIH and others to examine the drug discovery pipeline and identify and address systemic bottlenecks.

That motivation is the impetus behind the recent establishment of NCATS, which will build on ongoing translational research activities across the ICs. NCATS is not intended to be a drug company, but to address problems with the pipeline itself. Other NIH efforts in translational research include a partnership with the Department of Defense's Defense Advanced Research Projects Agency to build a biochip representing 10 to 12 different human tissues to test for drug toxicity, as well as collaborations with the pharmaceutical industry to rescue or repurpose drugs that are safe but have been set aside for lack of efficacy. The partnership between NIH and the FDA is another example of collaboration in the area of translational sciences.

Another area Dr. Collins mentioned is new research funding enabled by the Family Smoking Prevention and Tobacco Control Act. This law gave FDA unprecedented authority to regulate the manufacture, distribution and marketing of tobacco products. FDA wants to carry out that mandate in collaboration with NIH to be sure whatever is decided here is evidence based. There is a working group between NIH and FDA co-chaired on the NIH side by Drs. Tom Insel and Bob Croyle of the NCI. Following appointment of the soon-to-be named Associate Director for Disease Prevention/Director of the Office of Disease Prevention (ODP), which is part of DPCPSI, we expect to have the home for a lot of the coordination of this effort on tobacco research to reside in ODP, including the opportunity to prepare funding announcements to oversee research funding of tobacco control, to do portfolio analysis and to expand collaborations and partnerships.

As Dr. Collins pointed out, these opportunities can succeed only if NIH can recruit and retain the best and brightest minds in biomedical and behavioral research. Thus training is a continuing priority for NIH. At the June meeting of the NIH Advisory Council to the Director (ACD), reports will be presented by working groups commissioned to explore how NIH can best continue to contribute to the biomedical research workforce, as well as how to foster diversity in that workforce. Dr. Collins reminded Council of the paper published in 2011 noting the low percentage of African Americans, Hispanics, and Native Americans entering the biomedical research workforce and the lower success rates by African Americans in achieving independent awards among those who do go into research. He expressed concern about the overall poor job NIH has done in recruiting the best and brightest from all groups. Dr. Collins further noted that NIH does not have the data needed to model workforce needs for the future and that employment opportunities are constantly changing.

At present, NIH encourages recruitment and retention of talented researchers through Common Fund programs such as the NIH Director's Early Independence, Transformative Research, New Innovator, and Pioneer Awards. In addition, the Lasker Clinical Research Scholars Program invites physician-researchers to come to the NIH campus for

mentoring. Efforts are ongoing to improve the career pathway for women in biomedical careers, and although it does not have the authority to support education before the undergraduate level, NIH is exploring indirect opportunities to contribute to education at the high school level and below. Because the Office of Science Education (OSE) and the Science Education Partnership Award (SEPA) program have moved to DPCPSI, Dr. Collins proposed that Council form a working group to explore education in science, technology, engineering, and mathematics (STEM).

The remainder of Dr. Collins' remarks focused on the taxpayers' return on investment. The NIH budget doubled each year, from 1998 to 2003, and has remained flat since. However, when inflation is accounted for, NIH's actual purchasing power has declined and is now down 20 percent from 2003 levels. As a result, success rates for grant applications are at historically low levels. Dr. Collins stressed the importance of educating taxpayers and policymakers about NIH's critical role in solving the nation's health problems and the need for a budget that can sustain that role.

Dr. Collins also noted the role of NIH in encouraging the economy. In 2010, NIH supported 488,000 jobs at 3,000 institutions and small businesses nationwide, generating $68 billion in new economic activity. This new activity is double the taxpayers' investment. In addition, NIH serves as a foundation for the entire U.S. medical innovation sector, which employs 1 million U.S. citizens, generates $84 billion in wages and salaries, and exports $90 billion in goods and services. The Information Technology and Innovation Foundation reports that the United States' unquestionable dominance in science and technology has eroded since the 1980s, partly because of the rise of other nations and changes in funding and immigration policies. Dr. Collins pointed out that during the next week, when he meets with heads of other research organizations around the world, he will be the only one who expresses hope for a flat budget, while other nations will report how much they are increasing their investment in biomedical research. Dr. Collins, the President, and others have arguing for the United States to "out-build, out-innovate, and out-educate every other country."

Discussion Highlights

- It is not clear how the return on investment for NIH compares with that for other areas of spending, such as military base support.

- Most U.S. citizens do not know what NIH does, because public announcements and press releases of major discoveries focus more on the individual IC supporting that work and the grantee institution carrying it out. The Federation of American Societies for Experimental Biology has developed factsheets describing the NIH dollars awarded to institutions in and research being conducted in each state. However, more work is needed to increase the visibility of NIH.

- The President's Council of Advisors in Science and Technology has issued a report that proposes thoughtful solutions to challenges in STEM education.

- Efforts to repurpose abandoned drugs could prove useful for those that were abandoned by companies because there does not appear to be a market for them. NIH can support small efforts for such drugs, particularly for potential treatments of rare diseases.

- The Patient-Centered Outcomes Research Institute (PCORI) has recently issued a series of funding announcements and represents an opportunity for comparative effectiveness research (CER). This does not mean that NIH will abandon its own efforts. Rather, PCORI represents an expansion of them.

- Dr. Collins described his dream of a national network that would maintain the infrastructure needed for clinical research and link NIH, PCORI, the Agency for Healthcare Research and Quality, and health services organizations that have already implemented electronic health records and have research experience.

- NIH has several ongoing partnerships with the Department of Defense. One of the most visible projects is one to identify predictors of suicide among soldiers. NIH is also in discussions with the U.S. Department of Veterans Affairs.

- A vigorous search is ongoing for an NCATS director.

- In response to a question about other planned reorganizations, particularly in the current fiscal climate, Dr. Collins stated that the NIH Scientific Management Review Board suggested bringing together all substance abuse research (for example, tobacco research from the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the National Cancer Institute) under one roof. However, in light of the complexity associated with the establishment of NCATS and the dissolution of NCRR, how to merge substance abuse research at NIH is still under discussion and NIH would only want to take on those challenges if we are quite convinced that science would benefit as a result of the changes.

VII. THE NATIONAL PRIMATE RESEARCH CENTERS (NPRC) AND TRANS-NIH RESEARCH

Dr. John D. Harding stated that the NPRC program is the largest single program DCM supports and at present consists of eight Centers across the United States. Most of the NPRC base grants are more than 50 years old, highlighting the emphasis NIH has placed makingcentralized primate resources available to NIH-supported researchers. The NPRCs are also open to others who conduct research on non-human primates. NPRCs support all major areas of biomedical research, including infectious diseases, neuroscience, aging, cardiovascular disease, and cancer. Work with the animals is usually done at the Centers, and investigators can obtain information and samples to take back to their own laboratories; NPRCs sell animals only rarely.

With non-human primate colonies and associated husbandry, each NPRC is a centerpiece of knowledge about these animals. Each Center has a core group of doctoral-level scientists who manage the Center with the DCM base grants and conduct scientific

research with funding by the ICs. Each Center also offers core laboratories, a tissue and DNA bank, and training opportunities for graduate students, postdoctoral fellows, and veterinarians. NPRCs also engage in communication and community outreach; for example, they offer tours to their local communities to increase the communities' knowledge of the Centers.

NPRCs accounted for $86 million in total costs for DCM in FY2011, and in turn the eight Centers supported grants from 19 ICs. For every dollar provided by DCM, the NPRCs receive approximately two from cost-recovery, mostly from NIH grants. The NPRCs also leverage their resources by participating in an NPRC consortium, which is advised by the NPRC Directors and includes several working groups. Overall, NPRC funds support approximately 1,700 personnel, including 300 core scientists, and 1,000 research projects involving 2,000 scientists from outside the Centers. These activities generate about 700 peer-reviewed papers each year.

VIII. NON-HUMAN PRIMATE STUDIES FOR THE PREVENTION OF HIV INFECTION

Dr. Ronald Veazey highlighted activities and accomplishments of the NPRC at Tulane University, which uses the simian immunodeficiency virus (SIV) model in various macaque species to study early events in HIV infection. In a paper published in *Science* in 1998, he and other investigators reported that the gastrointestinal tract is an early site for SIV infection in nonhuman primates. $CD4^+$ T cells are depleted in the intestine, even as they remain stable in peripheral tissues. These findings were confirmed in HIV-infected humans 7 years later. Work at the Tulane NPRC has also suggested that activation of $CD4^+$ T cells expressing CCR5 drives viral replication, which eliminates the activated T cells, damages the mucosa, and allows bacteria to penetrate the intestine and further drive systemic immune activation. Although this hypothesis was controversial when first proposed, it is now an active field of HIV research. How $CD4^+CCR5^+$ cells are eliminated is still a subject of debate. Investigators at the Tulane NPRC also demonstrated the vaginal mucosa was also a major source of activated CD4+CCR5+ viral target cells and may be key to preventing vaginal HIV transmission.

Other work at the Tulane NPRC has shown that:

- Natural primate hosts do not have $CD4^+CCR5^+$ cells in the intestine and thus do not depend on these cells for immunity.
- Even after therapy, when SIV virus is undetectable in the blood, SIV RNA is still present in the intestine, which has also been confirmed in HIV-infected humans.
- Elevated progesterone levels increase susceptibility to vaginal SIV transmission, which was recently confirmed in humans.
- Blocking CD4 or CCR5 receptors can prevent vaginal HIV transmission.

Ongoing work in collaboration with Northwestern University is focused on tracking cellular events in HIV infection and pathogenesis. Other work is focused on dendritic cells, which might serve as a mechanism by which HIV is trapped in organ reservoirs, and on the development of vaginal rings containing microbicides to prevent transmission.

Discussion Highlights

- Progesterone levels increase during pregnancy, but to date, no work has explored progesterone-directed prevention of HIV transmission to the fetus.
- There is no large international organization of non-human primate centers, although such an organization would be worthwhile. Some countries, such as India, have stopped exporting rhesus macaques, which have been the workhorse of HIV research.
- The eight NPRCs often collaborate on infrastructure and share databases, and further scientific collaboration is under discussion.
- NPRCs have been proactive about preparing for natural disasters. The Tulane NPRC moved its animals before Hurricane Katrina struck, and NCRR provided support for generators after the storm. Other NPRCs in earthquake-prone zones have worked to meet construction codes.

IX. CONCEPT CLEARANCES

Common Fund Concept Clearance.

Dr. Elizabeth Wilder, Director of the Office of Strategic Coordination (OSC), described the process for concept clearances related to the Common Fund.

A. Common Fund Concept Clearance Process

The Common Fund aims to support areas of science where there are cross-cutting challenges or where recent discoveries have created new opportunities that can have a dramatic impact across a broad spectrum of science. The unique nature of the Common Fund has necessitated the development of a concept clearance process tailored to its overall purpose. Thus the process of concept clearance for Common Fund projects has evolved based on experience and on input from CoC.

Overall, the concept clearance process for the Common Fund considers whether the proposed concept addresses areas of science where the Common Fund should focus, whether the challenges are significant for a broad segment of health research, and whether opportunities exist for the Common fund to have a transformative impact. DPCPSI proposes a new process divided into two phases. Phase I, which is unique to the Common Fund, involves strategic planning to identify areas where NIH will make a concerted effort to exert a transformative impact. Phase II, which is similar to the concept clearance process of most ICs, involves DPCPSI and IC staff in determining what should be done for a program. DPCPSI is asking the CoC to provide its input during Phase I.

Dr. Wilder outlined four steps across the two-phase concept clearance process:

- DPCPSI gathers concepts from IC directors and staff, as well as through strategic planning meetings with external scientists. DPCPSI then triages these concepts, removing concepts that resemble existing programs or programs that have already been completed. The Division has gathered concepts for the past 6 months and narrowed the initial list from 67 to 37 concepts.

- DPCPSI provides a list of these concepts to CoC for review, discussion, and voting. For each concept, the Division provides a description of the scientific opportunity or challenge and goals, as well as a very rough draft of the proposed program. Dr. Wilder pointed out that concepts approved by the Council will undergo further planning and shaping.

- DPCPSI tallies votes. Those concepts that have received a majority of "yes" or "maybe" votes are deemed cleared. Comments provided by Council members will guide further development of the concepts, and the public will have an opportunity to comment.

- Concepts that have been cleared by the Council will be discussed by NIH leadership, and the NIH Director will select which ones will move forward for Phase II planning. This phase will involve analyses by OPA and trans-NIH working groups. Because each program will be managed by multiple ICs, the relevant IC Directors will review proposals and budgets, and the advisory councils for those ICs will provide secondary review.

Dr. Wilder noted that the concepts under review today could be implemented in FY2013 or FY2014, depending on how well they are articulated. She added that because so many concepts have emerged from Phase I strategic planning, the clearance process will be electronic. A social media site has been established to facilitate discussion among Council members as they review and vote. Council members also have received a spreadsheet where they can record votes, and they are asked to inform DPCPSI whether they prefer the spreadsheet or social media site.

As it reviews potential Common Fund concepts, CoC is asked to weigh whether the concept addresses an important trans-NIH topic, can create new paradigms, and can achieve its goals within 5 to 10 years. Members can vote yes, no, or maybe. Dr. Wilder clarified that a "maybe" vote indicates that the Council member thinks a concept might be useful but has suggestions for improvement. However, Council members can also provide comments on "yes" or "no" votes as well. Council responses and votes are due June 14.

Discussion Highlights

- DPCPSI intends to report to the Council as approved concepts exit the Phase II planning process. At present, the concept clearance process for Common Fund projects does not involve subsequent CoC input into the final implementation of a

concept. Although some Council members felt it might make more sense to bring a final list of planned concepts to the Council for final approval, they and DPCPSI acknowledged logistical problems with that type of review. Teleconferencing might be one way to address this challenge.

- Because of the large number of concepts, DPCPSI should consider assigning concepts to individual Council members to facilitate review and discussion. DPCPSI could also consider whether CoC could prioritize the concepts it approves. Assigning concepts might be difficult, however, because no concept aligns with any individual or subset of Council members.

- In their comments, Council members can question why a concept has been proposed for the Common Fund and not a particular IC. DPCPSI would also like to know when Council members' votes might depend on anticipated costs or when a concept might be better supported as a pilot project.

- For future concept clearance processes, CoC could have online interactions and an electronic vote to rank concepts, then spend time at the following Council meeting to discuss the concepts further.

- Once a concept has been cleared by Council, DPCPSI considers that concept as permanently cleared. Although it is possible that the Division could return to a cleared concept it previously did not have funds for, it generally does not consider its list of concepts a bank of ideas for the next 5 years.

- The point at which ICs commit to a Common Fund program varies across programs. However, ICs are expected to continue supporting a useful program once it leaves the Common Fund. With this expectation in mind, DPCPSI carefully crafts each program and involves several IC Directors as it plans for programs to transition out of the Common Fund.

The CoC then turned its attention to the review of the two ORIP concepts under consideration. Ms. Kawazoe reminded the Council that DPCPSI will ask for a motion, discussion, and vote and that concepts are cleared by a single majority. If a concept is deemed unlikely to achieve its goals, CoC will be asked for specific recommendations. Once these recommendations are incorporated into the proposed concept, the revised concept is not brought back to CoC for discussion.

Office of Research Infrastructure Programs Concept Clearances

Dr. Anderson and Dr. Franziska Grieder, DCM Director, emphasized that ORIP concepts are separate from Common Fund concepts, they will be funded from a separate budget, and concept clearance and review for ORIP concepts will be similar to that in the ICs. The Council of Councils will be asked to review and clear ORIP concepts for initiatives, and provide second-level review for applications received in response to these initiatives.

A. Division of Comparative Medicine (DCM)—Human Tissue and Organ Resource (HTOR)

Dr. Grieder noted that ORIP, like the ICs, must bring concepts for clearance before it writes its RFAs. Concepts receive approval for 5 years; thus ORIP will bring them back to the Council for clearance before they are renewed.

The HTOR has been funded for more than 25 years, most recently by NCRR. The resource procures, preserves, and distributes a broad range of normal and diseased human cells, tissues, and organs for biomedical research. The concept is up for renewal, as the last RFA was issued in 2007.

The proposed RFA will use a cooperative agreement mechanism (U42) and support an open competition for one award. The grant will be awarded in FY 2013 for 5 years, with a total cost of up to $1.5 million. DCM expects substantial Federal scientific and programmatic involvement in decision making for the resource.

A motion to approve the concept as proposed was forwarded and seconded. Discussion focused on the following points:

- The National Disease Research Interchange (NDRI), which currently runs the resource, distributes approximately 5,000 samples to 350 investigators per year.
- The proposed RFA is an open competition, but DCM expects that NDRI will write a renewal application.
- The proposed total cost does not include an increase in funding.
- The resource is not so much a repository as it is an exchange or procurement service. The awardee will serve as a conduit between procurers and researchers.
- There are other similar services offered by NIH, but these are highly specific, whereas the proposed resource is serving a broad range of research areas.

The motion passed unanimously.

B. Division of Construction and Instruments (DCI)—Developing and Improving Animal Resources

Dr. Elisabeth Koss described a G20 program that supports upgrades to existing animal facilities that support biomedical or biobehavioral research. This program was initially funded by NCRR in 1989 and transferred to ORIP in FY 2012. Awards made under this program assist biomedical research institutions in upgrading existing facilities, making alterations and renovations to improve laboratory animal facilities, and purchasing both fixed and movable equipment for these facilities. Both the number of applications and the success rate for this program have remained stable over the program's history.

The proposed concept would re-issue the RFA written in 2010, again under the G20 mechanism. Academic and biomedical research organizations or institutions would be eligible for these awards. About $7 million would be available for this program, and DCI anticipates 12 to 14 awards, with a cost of up to $500,000 per award.

A motion to approve the concept as proposed was forwarded and seconded. Discussion focused on the following points:

- With real purchasing power down by 20 percent since the end of the budget doubling in 2003, with the crisis ICs face in terms of paylines for research grants, and with talented people leaving research because of the current budget climate, NIH may have to make stark choices between people and bricks and mortar.

- Previous budgets for the proposed program were twice what it is now. The program budget was cut 50 percent four years ago, and award caps were lowered. For these grants, institutions receive only what is needed.

- It is not clear how much the implementation of new guidelines for animal care and use will affect programs like this one, but it is expected to be significant.

- This program has attempted to require matching funds in the past, but that is complicated because smaller institutions often do not have the capacity to match funds. However, lowering the amount of awards effectively pushes applicants to find matching funds.

The motion passed (21 for, 1 against, no abstentions).

X. UPDATE ON WORKING GROUP ON CHIMPANZEES IN NIH-SUPPORTED RESEARCH

Drs. Kent Lloyd and Daniel Geschwind, Council members, reminded the Council that the NIH Director had commissioned the Institute of Medicine (IOM) to conduct a study to assess the necessity of using chimpanzees in biomedical and biobehavioral research. In December 2011, IOM issued its findings and recommendations. The NIH Director accepted the recommendations, and the Council Working Group on Chimpanzees in NIH-Supported Research was established to determine how best to implement them. NIH also reported that it will not fund new projects for chimpanzee research until policies for implementation have been developed. In addition, a request for information yielded 110 comments from the public.

The Working Group is expected to:

- Develop a plan for implementation of IOM's guiding principles and criteria.

- Analyze currently active NIH-supported research using chimps to determine which ones meet IOM criteria.

- Advise on the size and placement of active and inactive populations that might need to be considered as a result of implementing IOM recommendations.

- Develop a review process to consider whether potential future use of chimpanzees is scientifically necessary and consistent with IOM principles.

Since it was formally established at the February Council meeting, the Working Group has held three teleconferences and one in-person meeting. Members have read and discussed the IOM report in its entirety to ensure all are familiar with it, including areas that are left intentionally vague. The Working Group has also received a debriefing by NIH staff on chimpanzee research, and it has established four subgroups aligned with specific themes and topics. Current NIH grants and contracts involving chimpanzees have been assigned to Working Group members for review, and the Working Group has visited two chimpanzee facilities to see the environment under which research, non-research, and active chimpanzee populations are maintained. The Working Group has reviewed and had some discussion of the 110 public comments NIH has received, and it has outlined major topic headings for its report and recommendations to the Council.

The Working Group hopes to have draft recommendations by the September Council meeting and a draft policy by the end of the year. A 60-day public comment is expected for the Working Group's report.

Discussion Highlights

- The Working Group's recommendations will be delivered to Council for its deliberation and approval before they are submitted to Dr. Collins. Dr. Anderson thus encouraged the Council to read and review the IOM report and public comments and to start thinking about its own questions and comments.

- One of the IOM principles guiding use of chimpanzees in research states that "there must be no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects." The phrase, "cannot be ethically performed on human subjects," is open to interpretation. For example, one might determine whether research in human beings is ethical depending on whether alternatives exist to research that places humans at risk. However, IOM has included in its report several cases related to this issue, and work in animal models does not necessarily eliminate the risk to human participants.

- Two NPRCs house chimpanzees. Other primate facilities in Louisiana, Texas, and New Mexico also have NIH-owned chimpanzees, and a Federal sanctuary houses chimpanzees retired from research.

- In addition to the request for information and publication of a notice in the *Federal Register*, consultants can also be brought in to help the Working Group's deliberations. These activities also allow for animal-interest groups to comment.

- The Working Group's recommendations will pertain only to chimpanzees owned or supported by NIH.

XI. UPDATE ON THE NIH OFFICE OF SCIENCE EDUCATION AND SCIENCE, TECHNOLOGY, ENGINEERING, AND MATHEMATICS (STEM) ACTIVITIES GOVERNMENT-WIDE

Dr. Anderson reminded the Council of the importance of STEM education in creating a pipeline of researchers, as well as of the correlation between mathematics achievement and subsequent economic, psychological, and health-related well-being and quality of life. For more than 120 years, the United States has led the world on many measures of educational attainment. Now, however, the Nation is no longer in the top 20% of industrial countries, and it is not among the top 20 nations in terms of college degrees. These trends have already begun to have negative consequences for the U.S. economy and the middle class.

The America COMPETES Reauthorization Act of 2010 calls for the White House Office of Science and Technology Policy (OSTP) to establish, maintain, and update an inventory of Federal investments in STEM education as part of a 5-year strategic plan. In December 2011, the White House National Science and Technology Council Committee on STEM Education (CoSTEM) produced its inventory and concluded that there were no areas of overlap or duplication. However, CoSTEM did highlight a need for better coordination and prioritization. The Committee's 5-year strategic plan, which will be released in September 2012, will focus on learning and engagement, educator and leader performance, post-secondary STEM degrees and STEM careers, institutional capacity, and educational research and development. STEM education for underrepresented groups is a cross-cutting theme across all these areas.

In FY 2010, investment in STEM education activities totaled $1.1 trillion, of which Federal investments totaled $3.44 billion. NIH is among the 13 Federal agencies that have invested in STEM education. However, most of its funding has focused on undergraduate students or higher. Only 5 percent of NIH investments have focused on education in kindergarten through twelfth grade, and the majority of that investment has come from OSE and the SEPA program. Working with NIH ICs and public and private organizations to develop and coordinate activities, OSE supports initiatives for students, educators, parents, and the general public. The SEPA program aims to bring active scientists and clinicians together with community groups, schools, and museums to increase the population's participation in clinical and basic research careers. Most of these activities are focused on training, as NIH is not authorized to fund education.

Now that OSE and SEPA are both part of DPCPSI, the Division can re-assess their investments and consider how best to support national STEM education efforts within NIH's mission and resources. Dr. Anderson requested approval to establish a Council Working Group to provide advice and recommendations on:

- Priorities for areas, activities, and opportunities where NIH is uniquely positioned to advance STEM education.

- How OSE and SEPA can have the greatest impact to enhance and coordinate current or new NIH activities in K-12 STEM education, keeping in mind that each IC has its own appropriation for educational activities.

- The role of OSE and SEPA in public education.

- How to leverage existing resources, currently totaling $28 million, to achieve the most significant impact.

The proposed Working Group will inventory and evaluate current activities and seek input from experts and stakeholders, and it will have the CoSTEM strategic plan to guide its deliberations. DPCPSI anticipates that enough will be known about the CoSTEM report for the Working Group to begin work in July 2012 and present its report and recommendations to Council and Dr. Anderson in early 2013.

A motion to approve the establishment of this Working Group was forwarded and seconded. Discussion focused on the following points:

- A request to make the NIH authorization more explicit with respect to STEM education has been approved by HHS and is pending in Congress.

- NIH has resources that could be applied indirectly to educating K-12 teachers through its investment in laboratories and research.

- In light of its limited resources for K-12 STEM education activities, DPCPSI should be highly selective and focus on a major goal, rather than duplicate activities.

- DPCPSI might be able to leverage its resources by working with Common Fund activities focused on career opportunities for biomedical scientists. NIH could also play a leadership role in supporting biomedical scientists who are interested in teaching at the K-12 level. Lessons could be learned from Germany, which has placed high social capital in its STEM teachers.

- The proposed Working Group should understand the landscape of STEM education fully, so that it can recommend NIH activities that are value-added.

- NIH should also consider the total infrastructure in which it has already invested and ways to leverage that for STEM education activities.

The motion passed unanimously.

XII. 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).[2] 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 reviewed 138 applications with total direct costs of $146,576,752.

XIII. CLOSING REMARKS

Dr. Anderson thanked Council members and speakers for their contributions at this meeting. The next Council meeting will be held on September 5, 2012.

XIV. ADJOURNMENT

Dr. Anderson adjourned the meeting at 4:30 p.m. on June 5, 2012.

XV. CERTIFICATION

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

6-29-2012

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

Date

6/29/2012

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

Date

[2] 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.