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)

NIH Council of Councils Meeting
November 16, 2009

Meeting Minutes

I. WELCOME

Lana Skirboll, Ph.D., Chair, welcomed participants, NIH staff members, and members of the public to the fifth official meeting of the NIH Council of Councils (CoC). The meeting opened at 9:01 a.m. on Monday, November 16, 2009, in Building 31, 6th Floor, Room 6, on the NIH Campus in Bethesda, Maryland.

A. Attendance

1) Council Members Present

Chair: Lana Skirboll, Ph.D., Acting Director, DPCPSI, OD, NIH
Executive Secretary: Robin I. Kawazoe, Deputy Director, DPCPSI, OD, NIH
Ronald L. Arenson, M.D., University of California, San Francisco
*Stephen L. Barnes, PH.D., University of Alabama at Birmingham
Enriqueta C. Bond, PH.D., Burroughs-Wellcome Fund (President Emeritus), Marshall, Virginia
Donna Bates Boucher, Bates Group, Inc., Denver
*Elizabeth B. Concordia, M.A.S., University of Pittsburgh Medical Center, Pittsburgh
*David W. Crabb, M.D., Indiana University School of Medicine, Indianapolis
Cecile A. Feldman, D.M.D., M.B.A., University of Medicine and Dentistry of New Jersey, Newark
Edwin Flores, Ph.D., J.D., Chalker Flores, LLP, Dallas
*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
Joseph H. Graziano, Ph.D., Columbia University, New York
Bevra H. Hahn, M.D., University of California, Los Angeles
Mary J.C. Hendrix, Ph.D., Northwestern University, Chicago
*Jean McSweeney, Ph.D., R.N., F.A.H.A., F.A.A.N., University of Arkansas Medical Sciences, Little Rock
Juanita L. Merchant, M.D., Ph.D., University of Michigan, Ann Arbor
Orien Reid, M.S.W., Alzheimer's Disease International and Consumer Connection, Laverock, Pennsylvania
Martin Rosenberg, Ph.D., Promega Corporation, Madison, Wisconsin
*David Valle, M.D., The Johns Hopkins University School of Medicine, Baltimore

*John W. Walsh, Alpha-1 Foundation, Miami
Gary L. Westbrook, M.D., Oregon Health and Science University, Portland
*Luther Williams, Ph.D., Tuskegee University, Tuskegee, Alabama
Marina E. Wolf, Ph.D., Rosalind Franklin University of Medicine and Science, North Chicago

*Appointment pending

2) Council Members Absent

Arthur M. Kleinman, M.D., Harvard University Medical School, Cambridge
Joseph Loscalzo, M.D., Ph.D., Brigham and Women's Hospital and Harvard Medical School, Boston
Daria Mochly-Rosen, Ph.D., Stanford University School of Medicine, Stanford, California
Richard A. Rudick, M.D., Cleveland Clinic, Cleveland, Ohio

3) Ad Hoc Representatives

Christine A. Bachrach, Ph.D., Acting Director, Office of Behavioral and Social Sciences Research, DPCPSI, OD
Barnett S. Kramer, M.D., M.P.H., Director, Office of Disease Prevention, DPCPSI, OD
Janine A. Clayton, M.D. Deputy Director, Office of Research on Women's Health, DPCPSI, OD
Wendy Wertheimer, Senior Advisor, Office of AIDS Research, DPCPSI, OD
Elizabeth L. Wilder, PH.D., Deputy Director, Office of Strategic Coordination, DPCPSI, OD

4) Presenters

Francis S. Collins, M.D., Ph.D., Director, NIH
Lawrence A. Tabak, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research
Antonio Scarpa, M.D., Ph.D., Director, Center for Scientific Review
Christopher P. Austin, M.D., Director, NIH Chemical Genomics Center, National Human Genome Research Institute
Dinah Singer, Ph.D., Director, Division of Cancer Biology, National Cancer Institute

5) NIH Staff and Guests

In addition to Council members and presenters, others in attendance included NIH Institute and Center (IC) Directors, NIH Office of the Director and IC staff, and interested members of the public.

B. Meeting Procedures

Ms. Robin Kawazoe reviewed the following:

- Each Council participant has completed and submitted a conflict of interest statement as a Federal requirement for membership.

- 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*.
- CoC members should not speak on the Council's behalf or on activities not yet cleared by Council.
- CoC has scheduled two *in-person* meetings per fiscal year, supplemented by emails, teleconference, and Web postings.
- The meeting minutes will be posted on the DPCPSI/Council's Web site.

C. Future Meeting Dates

Monday-Tuesday, March 22–23, 2010*
Monday-Tuesday, November 8–9, 2010

Monday-Tuesday, March 21–22, 2011*
Monday-Tuesday, November 14–15, 2011

Monday-Tuesday, March 19–20, 2012*
Thursday-Friday, November 15–16, 2012

*These meetings will be held if a need is identified at the preceding November meeting or by the NIH Director.

D. Announcements

- CoC members Mr. Robert Dickler, Dr. Dilip Jeste, Dr. Lenworth Johnson, Dr. Warren Jones, Dr. Marjorie Mau, Dr. Sandra Millon-Underwood, Dr. Sergio Ojeda, Dr. Harold Shapiro, and Dr. Phyllis Wise rotated off the Council effective October 31, 2009. Dr. Coleen Cunningham and Mr. Richard Chabran rotated off the Council 2 years early.
- Upon agreement from the Office of General Counsel, DPCPSI offices now have liaisons to CoC.
- A search for a permanent DPCPSI Director will begin soon.

II. REMARKS FROM THE NIH DIRECTOR: THE ROLE OF THE COUNCIL OF COUNCILS

Dr. Francis Collins, NIH Director, outlined five areas of opportunity he thought were ripe for scientific exploration:

- **Applying unprecedented opportunities in genomics and other high-throughput technologies to understand fundamental biology and to uncover the causes of specific diseases.** Dr. Collins noted, for example, that the ability to conduct inexpensive, high-throughput DNA sequencing has opened vistas of opportunities, including a project to sequence genomes from thousands of individuals with well-characterized phenotypes. Nanotechnology, nanomedicine, small molecule screening, and imaging were other examples. All these technologies allow opportunities that

emphasize comprehensive approaches such as The Cancer Genome Atlas, an exploration of genomics and the environment in autism, and a study of the human microbiome. However, these technologies also require robust computational muscle.

- **Translating basic science discoveries into new and better treatments.** Crossing the gap between basic research and drug development has long been the province of the private sector and will continue to be so for larger, more common diseases. However, NIH has opportunities for similar activities in rare and neglected diseases. These opportunities are afforded by new discoveries regarding the fundamental basis of disease. More is known about the molecular basis of genetic diseases, and academic researchers can further explore the pathways involved. By supporting these researchers, NIH can reduce the risk associated with translation and carry these projects far enough such that compounds that show promise might be more attractive to the private sector. For example, the NIH Roadmap has provided academic investigators with access to high-throughput screening capabilities similar to those employed by the pharmaceutical industry (see the presentation on Molecular Libraries, below). Small molecules, gene therapy, human embryonic stem cells, and induced pluripotent stem cells are all exciting developments in the realm of translational research.

- **Putting science to work for the benefit of health care reform.** In light of current efforts to transform the health care system, more evidence will be needed to determine which interventions are most effective. Although various NIH Institutes and Centers have long funded such studies, funds from the American Recovery and Reinvestment Act (ARRA) now support a ramping up of these efforts. Comparative effectiveness research (CER) as well as research on prevention, personalized medicine, behavior, health disparities, and pharmacogenonomics (getting the right drug at the right dose to the right person at the right time) will be critical parts of efforts to reengineer health care in this country. Also needed is a focus on large-scale prospective studies that can collect information about genetics and the envrionment in a way that is less biased than retrospective studies. The National Children's Study which is in a pilot phase will also require decision making about what the full-scale study might look like. Further analysis of health information technology (IT) and health economics research are also areas of need and considerable interest.

- **Encouraging a greater focus on global health.** Interest in global health is growing across the scientific community, particularly among younger investigators. Much has been learned about the pathogens causing a lot of the disorders in the developing world, and recent scientific advances make attacks on infectious disease more feasible than ever. Genomes have been sequenced for several pathogens, and through the National Institute of Allergy and Infectious Diseases (NIAID) and the Fogarty International Center, NIH have been involved in a large amount of work on AIDS, malaria, tuberculosis, and other, neglected tropical diseases. More study is needed to translate that knowledge into new preventive and therapeutic strategies. In addition, research must address the growing number of non-communicable disorders, such as cancer, injury, and heart disease, in the developing world. NIH has an opportunity to

play a role in coordinating research and identifying interventions that can be effective in areas where resources are limited.

- **Reinvigorating and empowering the biomedical research community.** Financial support of investigators continues to be a concern. ARRA has made it possible for researchers to propose bold ideas for Challenge and Grand Opportunity grants. More than 20,000 researchers applied for Challenge grants, and $5 billion was awarded on September 30. In light of the assumption that one NIH grant creates seven jobs, we calculate that all-together NIH ARRA-supported programs will create 50,000 jobs in the course of 2 years. However, it is not clear what will happen in FY 2011, when ARRA funding ends. Whether there will be a situation of a feast followed by a famine is unknown at this point because the budgetary decisions have not yet played out, and in fact, they are being deliberated right now in the Administration. How to prepare for softening that blow is under discussion.

Dr. Collins then discussed the Common Fund, which now includes over $500 million of research money. Although most of this money is committed at the present time, Dr. Collins noted that the time is fast approaching when NIH will have opportunities to support new and bold directions. In preparation for that time, NIH should rethink about where the Common Fund should go and assess its process for identifying new projects; want to ensure that innovation is a strong part of what we do. In that regard, one-third of the Common Fund supports awards that are focused on innovation: Pioneer, New Innovator, and Transformative R01 (T-R01) awards.

Dr. Collins also noted that NIH is in the process of assessing changes that have beeen made to peer review, and this will be an ongoing process. In addition, training programs need to be emphasized, including efforts to nuture early-stage investigators. NIH also needs to enhance its programs directed to minorities to help ensure a more representative biomedical workforce.

Dr. Collins then remarked on the CoC's role in the advisory process, specifically as it relates to the Common Fund. Additionally, he briefly noted the other advisory groups that interact with the NIH Director:

- The Advisory Committee to the Director (ACD), which addresses problems where the NIH Director feels attention is needed. ACD establishes working groups to focus on certain tasks.

- The NIH Director's Council of Public Representatives (COPR), which comprises individuals from the public. COPR provides input about areas the public feels should be addressed by NIH, serves as a valuable source of information, and provides a means for NIH outreach.

- The Scientific Management Review Board (SMRB), which was mandated in the NIH Reform Act of 2006. SMRB assesses the organizational structure of NIH and makes recommendations for changes. For example, SMRB is exploring ways to address the challenges faced by the Clinical Center as a hospital, in light of constraints on the

Intramural Program budget. The SMRB is also looking at the possibility of merging two Institutes that have a fair amount in common – the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Acohoism

The NIH Council of Councils, which was also established by the 2006 NIH Reform Act, assesses the Common Fund and the policies and activities of DPCPSI, particularly whether the research that is being planned is responsive to emerging opportunities. The Council also carries out second level review for programs like the Transformative R01 awards. Council members are asked to bring their knowledge of their individual ICs' missions and operations, not as official representatives, but to form a coalition to build broader advice. In this capacity, CoC members should explore and provide advice beyond the research agenda of any one IC. In the past, CoC has assessed the former Office of Portfolio Analysis and Strategic Initiatives; the Research, Condition, and Disease Categorization (RCDC) system, which now resides in the Office of Extramural Research (OER); the T-R01 program; and early concept clearance of programs proposed for the Common Fund.

At present, as mentioned earlier, one-third of the Common Fund is allocated to high-risk, high reward (HRHR) projects; resources, such as the Molecular Libraries project, to foster discovery and translation; interdisciplinary research; a microbiome project; and the Genotype-Tissue Expression (GTEx) project. Thus funds are available only to support workshops and pilot projects; there are no resources available for placing new projects on the on-ramp. In addition, NIH, with the help of CoC, will have to ensure that existing Roadmap projects continue to receive support to the extent they still fit the mission and purpose of the Common fund. NIH must also decide how to handle Common Fund projects that have become highly successful but have no clear IC home at the end of a 5-year, and in some cases 10-year, funding period. This problem is especially complicated in light of the budget constraints faced by individual ICs. Dr. Collins pointed out that Common Fund priorities do not focus on any one disease, but are purposefully broad. He also expressed the desire to ensure the Common Fund is nimble enough that new projects are not impeded by excessive layers of decision-making.

Dr. Collins closed by asking CoC to consider how the Common Fund should proceed in the long term. The Council should consider how to identify the most exciting grand challenges with potential to transform health and medicine, as well as how best to gather input from the big thinkers within and outside NIH. Specific areas to consider for the future include:

- Therapeutics for Rare and Neglected Diseases (TRND) and Rapid Access to Interventional Development (RAID) programs.
- Projects, including clinical trial design, that can be done in collaboration with the U.S. Food and Drug Administration (FDA).
- Efforts to address neglected tropical diseases, in collaboration with other global health organizations.
- Education in science, technology, engineering, and mathematics (STEM).

- Expansion of GTEx.
- Connectivity map projects, which were presented at the November 2008 CoC meeting.
- Workshops on biobanking, particularly an assessment of the United Kingdom Biobank.
- Health economics research.
- Protein affinity reagents.
- Mouse phenotypes.
- Collaborations with health maintenance organizations.
- Translational stem cell research.
- The science of behavioral change.

Discussion Highlights

- The relationship between the NIH Director and CoC is still a work in progress. Dr. Collins welcomes comments from Council members on how to develop a clearer role for the CoC.
- NIH is considering how best to report its progress in using ARRA funds. The agency has a history of reporting outcomes, but this is the first time it will report progress on an investment. Several avenues of information will be available to show that ARRA funds have been invested in science, not just equipment.
- Part of the effort to alleviate the effects of the post-ARRA "cliff" will require an emphasis on the science. Dr. Collins noted that, in his experience, the biomedical research community most successfully makes its case to Congress when it describes the promise of science and how research support has improved human health. NIH will have to document how its funding serves as a good stimulus. NIH also will have to communicate its successes to the public, who can influence Congress. COPR has a clear role in engaging and informing the public of the value of NIH.
- Some Common Fund projects will result in commodities to which a potential value can be attached. However, commercialization of sunsetting Common Fund projects will have to be assessed on an individual basis to ensure continued availability to academic investigators and to those focused on rarer diseases.
- One Council member noted the need to develop a set of indicators or criteria to guide decisionmaking regarding the Common Fund. This member also expressed concern that CoC might not be in the best position to assist with that process, and because monies are no longer contributed to the Common Fund by the ICs, she requested a clarification of the role of the Council.

- Traditionally, science has taken snapshots of discrete moments in a disease, but some questions or areas of study, for example epigenetics, require a much longer time period. One Common Fund project is focused on epigenomics, and other projects to follow the long-term effects of prenatal marks are under discussion.

- Population-level research, while resource intensive, could provide comprehensive information and stimulate several other research projects. Without such research, the biomedical research community will continue to depend on disease-specific prospective studies and be unable to capture the full spectrum of opportunities.

- Several programs have been designed to promote diversity in the biomedical workforce, but institutions have not been held accountable for failure. NIH has a group reviewing these programs.

III. UPDATE ON THE AMERICAN RECOVERY AND REINVESTMENT ACT (ARRA) FUNDING AND THE COMMON FUND ARRA PROJECTS

Dr. Lawrence Tabak, Director of the National Institute of Dental and Craniofacial Research, provided an overview of ARRA funding activities. ARRA appropriated $10 billion to NIH: $8.2 billion was used for extramural scientific research; $1 billion for extramural improvement and construction through NCRR; $300 million for extramural scientific equipment; and $500 million for buildings and facilities on the NIH campus. In addition, $400 million was appropriated to NIH via the Agency for Healthcare Research and Quality (AHRQ) to support CER.

In administering these funds, NIH aimed to stimulate, accelerate, and expand biomedical research using a blend of existing mechanisms and new programs. This blend is particularly important to ameliorate the post-ARRA funding cliff. To accelerate the science of existing programs, NIH solicited applications for administrative supplements (including a summer program). Support for new science includes funding additional meritorious applications (RO1s, R21s, and R03s) that have been peer reviewed and approved by IC Councils ("Payline Extension"), revisions to extant programs ("competing and administrative supplements"), and new ARRA NIH-wide and IC-specific programs. The latter category includes Challenge Grants and Grand Opportunity grants.

Although there has been an outcry from the scientific community regarding the low success rate for Challenge Grants, NIH was able to fund 840 applications, many more than originally projected, and several Challenge Grants were supported with CER funding. Grand Opportunity grants had a healthy success rate, and more than 1,300 awards were made for the summer program, supporting approximately 5,000 positions.

Competitions for funding opportunities supported by FY 2010 funds have closed, and reviews are underway. These opportunities include a new technology pilot program, a program to catalyze entry of new small businesses, an academic research enhancement award, a program geared toward building sustainable research communities, NCRR-administered supplements, and an NIAID funding opportunity announcement (FOA) on

protecting human health through immunology and vaccines. Dr. Tabak invited Council members to sign up at the OER Web site for email alerts about additional funding opportunities.

Dr. Tabak concluded by reminding the Council of the many reporting requirements associated with ARRA-supported projects. Data from these reports will be used to populate Recovery.gov, which allows the public to track how ARRA funds are spent. NIH ARRA investments also can be tracked through RePORT. Dr. Tabak acknowledged the President and Congress for their confidence in NIH, the NIH staff who worked long hours to ensure ARRA funds were disbursed in a timely manner, and CoC members who served as reviewers while preparing their own applications.

Dr. Elizabeth Wilder, Deputy Director of the Office of Strategic Coordination, discussed the Common Fund, which received a proportion of ARRA funds representative of its proportion of the overall NIH budget. Unlike past Common Fund initiatives, which resulted from long periods of strategic analysis, ARRA-supported Common Fund activities required rapid decision making. DPCPSI decided to spend the bulk of these funds on new projects, in line with the stimulatory goals of ARRA. New awards were made through 2008 and 2009 FOAs, Challenge Grants, Grand Opportunities Grants, and New Innovator awards. Challenge Grants and support for new innovators formed 80% of the ARRA funds used by the Common Fund. Remaining funds were spent on expansion of existing programs where high-priority needs could be identified

Dr. Wilder noted the following scientific areas that received ARRA funding through the Common Fund:

- Stem cells, including factors controlling differentiation in complex environments; insights, methods, and reagents for nuclear reprogramming of human stem cells and effective induced pluripotent stem cells; humanized mouse models; and translation.

- Epigenetics, and particularly the development of new technologies in protein arrays, computational tools, high-throughput screening, micro RNAs, and identifying small molecules that bind proteins involved in modifying histone structure.

- Behavioral change and how it works. Projects include development of a computer system that interacts with cell phones, an assessment of whether providing nutritional information works alone or in conjunction with subsidies, and an exploration of whether cues in the home environment affect how much children eat.

- High-throughput screening, including genomics to identify small molecules in several assays, the development of a test to screen three-dimensional cultures of human cancer cells, and tests to identify inhibitors of the malaria parasite.

- Science, Technology, Engineering and Mathematics (STEM) education, specifically an assessment of which educational tools work in the community. Examples include efforts to improve the problem-solving performance of third-graders with math difficulties, an assessment of whether the inclusion of engineering curricula in

elementary school improves technological literacy and promotes positive attitudes about engineering, and an assessment of the long-term impact of placing scientists in middle-school classrooms to enhance learning and teaching.

Discussion Highlights

- Taxpayers also should be acknowledged for their support of ARRA.

- NIH's efforts to disburse ARRA funds as quickly as possible showed that awards can be accelerated and that science can therefore happen more quickly. However, the positive aspects of such acceleration must be balanced with its costs. NIH can learn from this experience and apply the positive attributes to future mechanisms.

- Several applications were received from individuals who had never approached NIH for funding, suggesting a large amount of enthusiasm in the research community.

- CER funding has been one of the most visible aspects of the ARRA funds allocated to NIH. It will be tracked carefully in terms of how this money is spent and how research results are used.

- NIH is considering effective communications strategies to inform the public about what has been funded. Council members suggested a large workshop where key individuals would report on ARRA-supported projects. Posting project video clips on the DPCPSI Web site or on YouTube was also suggested. Social networking is under exploration. Council members emphasized the need to ensure that the research community, the health care sector, and the public understand the same messages. CoC and COPR could help in this aspect.

- It is not yet clear whether STEM education will represent a growth area for NIH. Present efforts aim to understand when children become interested in science, when they become discouraged from pursuing science or decide it is worth pursuing, and when they are directed toward some type of science literacy.

IV. RESULTS OF SURVEY OF "ROADMAP TRANSFORMATIVE R01 PROGRAM (T-R01) APPLICANTS AND REVIEWERS

Dr. Antonio Scarpa, Director of the Center for Scientific Review (CSR), discussed the review processes for the T-R01 and ARRA-supported programs and provided an update on NIH's overall effort to enhance peer review. More than 700 applications were submitted and reviewed for the T-R01 program, and of those, 42 were funded. Review involved an editorial model, where "editors" provided a detailed scientific review during the first round, applications that passed that round were forwarded for a mail review (stage 2), and all editors participated in an in-person meeting to review the big picture and broad impact following the mail review. Resulting scores fell into a traditional Gaussian distribution.

In a survey, more than half the editors responded that it was reasonable for them to read at least two pages of an application and provide an initial score. They agreed that most of the applicants understood the goals of the T-R01 program, although only 10% to 25% of the applications were truly transformative. In addition, the editors agreed that stage 2 reviewers also had a good grasp of the goals of the T-R01 program.

About 80% of the applicants were male, and the racial and ethnic distribution among these applicants mimicked what NIH experiences overall. However, the age distribution appeared to be somewhat improved; applicants for the T-R01 program were younger than were those for other programs. About 90% of applicants had experience with grant-writing for NIH, and the majority already had grants from NIH. In the survey, 82% responded that their T-R01 applications represented a significant departure from what they usually do. They felt that the challenges, impact, approach, and appropriateness of the applications were more important than the bibliography, abstract, or timeline, and they felt that this program was special and that they could not have written similar applications for any other.

Dr. Scarpa then moved from the T-R01survey results to an update on the Enhancing Peer Review initiative. With respect to enhancing peer review, all of the proposed changes except for shortened application length now have undergone two cycles of review.

- The core review criteria have been changed to emphasize the application's significance, the investigator, innovation, approach, and environment. Although the review emphasis has changed to focus first on whether a problem is worth exploring, most applicants are still used to spending the bulk of their time on describing their approach.

- Template-based critiques have received some criticism, as some reviewers have continued to simply describe the application or have written nothing on the templates. A CSR study is underway to further assess how these templates are used.

- Application scores have fallen into a linear distribution, although that curve has changed somewhat between the first year and the second. There is still some concern that scores will start to cluster again as reviewers learn the system.

- The order of review is now based on average preliminary scores, and reviewers thus must participate in the entire meeting. This change has been successful.

- Much time has been spent orienting CSR and NIH review staff, chairpersons, and reviewers, and this overall review of implementation has been successful. Scientific Review Officers (SROs) and study sections appear to understand the spirit of the new process. CSR is now filming a mock study section and will post that film on its Web site.

In 2008, 77,000 applications were received, and 75% of those were reviewed in a process that included 16,000 reviewers, 1,600 review meetings, and 240 SROs. By the end of FY 2009, and partly because of ARRA, more than 115,000 applications were received and

reviewed in a process that included 38,000 reviewers, 1,800 meetings, and 240 SROs. With the addition of ARRA and the time constraints imposed on review and distribution of ARRA funds, NIH staff had to contend with a two- to threefold increase in the number of applications during the summer of 2009. In addition, different programs had to be reviewed in different ways, but through parallel systems. Dr. Scarpa expressed appreciation for the extraordinary amount of work done by the staff this past summer.

Dr. Scarpa closed by noting that the number of submitted R01 applications appears to be constant, despite a spike in October. However, it is not clear whether many of the grants that were not funded by ARRA-supported programs will come back as R01 or R21 applications.

Discussion Highlights

- It might take some time for unfunded T-R01 applications to be submitted as traditional R01 applications, as investigators might have to reassess and reconsider preliminary data before resubmitting.

- The compression of page limits for R01 applications will represent a cultural change both for applicants and reviewers. However, some programs, such as the T-R01 and Challenge grants, have already had stricter page limits.

- For the scores in the bottom quadrant, which are most likely to be funded, NIH might want to consider reapplying a cumulative distribution to better see changes and differences among applications.

- CSR might conduct a study to assess potential differences in review outcomes between reviewers who express their thoughts in bulleted form and those who simply repeat or describe what is written in the application. Some Council members expressed concern that the shift to provide less detail makes it more difficult for applicants to improve their competitiveness.

- CSR suggests the use of more editors in the T-R01 review process and intends to add clinical investigators as study section co-chairs.

- Differences in how clinical and basic researchers define "transformative" or "high risk" should be considered, so that more clinical investigators can be encouraged to apply for these programs.

- CER and behavioral economics research are already underway to assess the dissemination of scientific discoveries to the community, but the T-R01 might foster innovative or transformative methods for dissemination. Liaisons are needed to provide community physicians with a resource where they can learn about the latest treatments.

- The editorial review process appears to work well for programs in which the science is particularly complex. NIH might also consider a triage or pre-application process,

although researchers/editors, and not program staff, should be responsible for deciding which applications should move on to full review.

- Because the data are not in for the T-R01 program, the breakdown among basic, clinical, and translational applications is not known. However, it is likely that these applications will be skewed toward basic science because of the way "transformative" was defined and framed. For the new round, the program has been redefined to encourage more clinical applications.

- Although the Common Fund generally applies to projects that directly or indirectly affect multiple ICs, the HRHR section of its portfolio (such as the T-R01 program) is not held to the trans-NIH model. NIH acknowledges the difficulty in developing transformative projects that touch multiple ICs. In addition, NIH does not aim to ignore existing programs, but it aims to acknowledge all contributions to science, both risk-taking and incremental building.

- During the second-level review of T-R01 applications, it became clear that CoC members brought different experiences and expectations regarding second level review. DPCPSI will consult with Dr. Collins and provide clearer instructions for the next round of T-R01 applications.

V. SCIENTIFIC PRESENTATION—MOLECULAR LIBRARIES ROADMAP

Although genomics and proteomics has yielded more knowledge about ourselves than ever before, and despite increases in spending devoted to drug development, more effort is needed to improve the translation of genomic discoveries into biological insights and therapies. About 1,900 molecular causes have been identified for Mendelian genetic disorders, but few of these causes have therapies associated with them. In addition, the genetic basis for many of the 6,000 rare or orphan diseases is known, but treatments are available for less than 200 of them. Dr. Christopher Austin, Director of the NIH Chemical Genomics Center, discussed the Molecular Libraries Program, which arose from an urgent need to determine the functions of genes and catalyze the development for rare and orphan diseases.

The Genome Project has shown that the number of proteins, rather than the number of genes, confers organismal complexity. Thus, the development of therapies should take advantage of the level at which Mother Nature works. Small molecules, a heterogeneous group of organic chemicals consisting of carbon, nitrogen, sulfur, and some halides, act on proteins and can be used to manipulate biological systems without exerting excessive toxicity. The Molecular Libraries Program aims to empower the research community to use these molecules in their research as perturbations or as starting points for drug discovery.

The pilot phase of this project included technological development, production, and data analysis and dissemination. Molecular library screening centers were established and fed by a central compound repository, and the National Center for Biotechnology Information (NCBI) built PubChem, a GenBank analog for small molecules. In addition,

Chemoinformatics Research Centers were established to develop tools and browsers and to hire the staff needed for data analysis. The Molecular Libraries Program is now in its formal phase through 2013. This phase involves diversity expansion, assay development and screening, development of instrumentation, and the generation of data and chemical probes. PubChem and the Molecular Libraries Probe Centers Network (MLPCN) continue to analyze and disseminate data, and other centers have taken over the work begun by the Chemoinformatics Research Centers, which were not renewed for this phase. PubChem includes 1,250 bioassays and 45 million substances representing 17 million to 18 million compounds, and the Molecular Libraries repository contains about 350,000 compounds collected under contract with BioFocus. MLPCN has invited individuals from both the public and private sectors to help it achieve a gold standard, genome-wide collection of small compounds. More information can be found at http://www.mli.nih.gov.

Dr. Austin noted that the Molecular Libraries Program is obligatorily collaborative; projects require biologists, chemists, computer scientists, and engineers and only work when these individuals are mutually dependent on each other. Investigators contact a center with an idea about a target, gene, phenotype, or disease and request small molecules that can modulate those targets. In collaboration with the investigator, the center develops and optimizes a high-throughput screening assay, then uses that assay to screen the small molecule repository. These efforts result in a chemical probe that meets criteria established by the collaborators; data are deposited in PubChem, and the investigator obtains the probe to generate data. All probes are available on the Molecular Libraries Program Web site.

The Program includes the NIH Chemical Genomics Center, which was founded in 2004 and is administered through NHGRI. This Center develops chemical probes for neglected diseases, for targets that are risky or difficult to work with, or as starting points for drug development. The Center includes biologists, medicinal chemists, and information technologists or computer scientists, the majority of whom come from the pharmaceutical industry, and these individuals work to make technology state of the art. Unlike other centers, the NIH Chemical Genomics Center screens compounds at seven to fifteen different concentrations to reduce the number of false positives from high-throughput screening. Thus, Center screens produce dose-response curves and activity profiles, and they establish an informatics pipeline for data processing, curve-fitting and classification, and extraction of information about structure-activity relationships.

Dr. Austin emphasized the importance of the Program being a trans-NIH initiative. The type of science involved in the Molecular Libraries Program is expensive and capital intensive. In addition, most of the targets assessed affect multiple systems, and compiling all the data into one database allows investigators to identify commonalities. To provide examples, Dr. Austin described projects focused on DNA repair, spliceosome abnormalities, pyruvate kinase activators, Gaucher's disease, and *Schistosoma mansoni*.

Dr. Austin also pointed out that academia has an advantage over industry because academic investigators devote their entire careers to a problem and thus know more about it. He further speculated that such an endeavor as a project in the Molecular Libraries

Program might not occur within the pharmaceutical industry because no biologists with relevant expertise have been included. Although the development of chemical probes is just a start in drug development, Dr. Austin noted that the handoff from the public to private sector previously occurred at target identification and that the Molecular Libraries Program can now provide drug development with a better starting point, analogous to a football team starting with better field position and thus having a better chance for a touchdown.

Dr. Austin closed his presentation by briefly discussing the Therapeutics for Rare and Neglected Diseases (TRND) project. Pharmaceutical companies tend to be reluctant about pursuing compounds for rare and neglected diseases, because the return on investment is smaller. TRND is intended to do for these diseases what the Molecular Libraries Program has done for the transition from target identification to development of chemical probes. Although the program is still in the starting phase, it will take advantage of the best aspects of academia and the pharmaceutical and biotechnology industries, with the goal of taking compounds far enough to entice other organizations to take them on. NIH has been engaged in several discussions with foundations and the biotechnology and pharmaceutical industries to determine the criteria for such compounds.

Discussion Highlights

- Through several discussions with its advisors, the Molecular Libraries Program collection was set up to be highly representative of the chemical space and to include compounds close enough to the biological space to be useful. This effort includes chemical diversity and natural products.

- The Program has screened its entire collection for several toxicities. In addition, the National Toxicology Program, which represents a collaboration of the NIH, the Centers for Disease Control and Prevention, the Food and Drug Administration, and other agencies is screening thousands of compounds, including those approved by several regulatory agencies, across a broad spectrum of assays.

- The Molecular Libraries Program has established a clearly needed infrastructure, but it is not clear where the program will go at the end of Common Fund support. This challenge relates to Dr. Collins' discussion of how best to maintain projects that are needed across ICs, while maintaining space for new projects. Several models have been discussed.

- NIH is still trying to determine how best to prioritize the rare and neglected diseases. One approach could involve an RFA inviting compounds that fit certain criteria, but there has to be an ongoing culling of projects that do not make headway. Another approach could involve placing data for all diseases in a database and identifying common physiological pathways, so that projects that work for multiple diseases could be supported.

- In the beginning, TRND will be small and include only two to three programs. However, expansion is possible.

VI. PORTFOLIO ANALYSIS—AN EXPERIMENTAL SPACE

The NIH Reform Act of 2006 states that the mission of DPCPSI is to identify research that represents important areas of emerging scientific opportunities, rising public health challenges, or knowledge gaps that deserve special emphasis. Implicit in this mission are two functions:

- To develop the capability to extract novel concepts and knowledge from the scientific achievements represented in the research portfolio to identify emerging areas of research and scientific opportunities. This requires computational approaches that do not exist yet.

- To disseminate this capability NIH-wide, both to the OD and the ICs. This involves disseminating the knowledge and assisting with analysis.

Dr. Dinah Singer, former Acting Head of Portfolio Analysis, DPCPSI, and currently Director of the Division of Cancer Biology, NCI, provided an update on portfolio analysis in DPCPSI. In the context of DPCPSI, portfolio analysis is defined as a knowledge and discovery endeavor, as the electronic integration and analysis of data from NIH research portfolios and other sources to identify emerging concepts and areas, opportunities, and gaps in research that will assist program strategic planning of future areas of NIH support. Portfolio analysis involves the use of computational algorithms to inventory applications in a portfolio, derive concepts embedded in those applications, and identify knowledge that could be generated from those concepts. Thus, portfolio analysis is an intermediate step between reporting and evaluation. Reporting tools are used to extract data, computational algorithms are used to analyze the data and derive new understanding, and evaluative decisions are based on that analysis.

With that definition, NIH established a Portfolio Analysis Group (PAG), which includes computational scientists, within the Office of the DPCPSI Director. PAG reflects the mission of DPCPSI by supporting research in and development of emerging areas of knowledge assessment and portfolio analysis and by serving as a resource on scientific, data analysis, and information technology tools for all of NIH. PAG interacts with:

- The OER Division of Information Services, Reporting Branch, which ensures the quality and integrity of data from the NIH grants portfolio, responds to requests for reports, and develops online statistical models and visualization tools for the extramural program. The Division does not perform analysis on its reports. PAG relies on the Branch to provide data and is working with the Branch to develop new capabilities and fingerprints.

- The Center for Information Technology (CIT) High-Performance Computing and Informatics Office, which provides the scientific community with expertise and research in high-performance computing, computational science, biomedical informatics, and modern information technology. PAG collaborates with the Office to develop new computational algorithms, using tools such as text mining, artificial intelligence, and natural language processing.

- The NLM National Center for Biotechnology Information (NCBI), which develops research-related resources and performs text mining and predictive analytics. PAG engages in one-on-one interactions with NCBI and participates in its seminars.

DPCPSI has performed two needs assessments to prioritize its activities in establishing portfolio analysis. In response to these assessments, DPCPSI has hired staff with strong scientific credentials and an interest in portfolio management to develop analytical applications. The group currently includes three biomedical scientists, three computational scientists, one data analyst, and one support staff person. DPCPSI also has assessed available analytic capabilities and incorporated them into PAG. The Group is now reviewing these capabilities and making necessary modifications.

Dr. Singer described four pilot projects that are underway. The first is using a retrospective analysis of grant applications from 2003-4 to validate an algorithm that identifies HRHR projects. The second is an analysis of trends and emerging areas in lung cancer. This project aims to determine what the major topics are now and what they were 5 years ago, how the portfolio is evolving and whether projections can be made about where it will go, how these changes are reflected in research, and what resources are available to get to the core of these issues. The third project tracks broad areas of translational research, and the fourth is a retrospective analysis to determine what areas of prior knowledge were necessary to develop the respiratory syncytial virus and how to track those areas.

The needs assessments also called for training and outreach in portfolio analysis, and several approaches have been employed. PAG has weekly staff meetings to share information and discuss projects and challenges, and it has developed a training manual and established an internal SharePoint site to exchange information and resources. For NIH overall, DPCPSI is developing a tools Web site to provide information to the community, and it will train staff and conduct analyses for OD and ICs. The PAG has undertaken an initial analysis of NIH CER activities. In so doing, it has learned that analysis is limited by the ability to extract valid datasets, which in turn is limited by the definition of a topic, the ability to include complex concepts in query tools, and differences in the way a consensus definition is interpreted.

Finally, the needs assessments recommended that ongoing input be obtained from subject experts and others. Focus groups have been convened within NIH to determine what is needed and wanted in terms of portfolio analysis. Dr. Singer acknowledged that these groups were not very successful because of time constraints imposed by ARRA activities.

Future plans include a think tank of experts in knowledge analysis and management, to be held in spring 2010. DPCPSI also plans to expand its collaborations with CIT, OD, and the ICs and to develop a training plan in which NIH staff can rotate through PAG to learn analysis technologies and tools.

Dr. Singer concluded by asking CoC for feedback on what criteria to use to prioritize projects; how portfolio analysis can be helpful to the Council in the future; how to

respond to queries from outside NIH; and what information could be useful to Council, to management of the Common Fund, and to specific ICs.

Discussion Highlights

- DPCPSI's efforts in portfolio analysis could be applicable to a wide variety of organizations, and the Division would like to eventually pull data from sources outside NIH.

- The most successful analyses of large databases have been simplistic; increased sophistication does not appear to help. NIH should develop keywords that are specific to the scientific community and include the vocabularies of different institutions and investigators.

- Rather than reinvent the wheel, DPCPSI should build on and modify existing tools. One goal of the 2010 think tank will be to talk with experts in different tools and determine how those tools can be applied toward the NIH research portfolio.

- The pilot projects must be pursued rigorously and validated to understand how to interpret the results of analyses.

- DPCPSI portfolio analysis is meant to inform, rather than direct, and to complement the efforts of the program managers.

- Providing different instructions on what should be reported might be helpful in developing tools for portfolio analysis. However, it is also possible that some analytic tools could circumvent differences in definition.

- Portfolio analysis is distinct from assessments of disease burden. Portfolio analysis will assess how NIH is investing its resources with respect to disease burden.

- Analytic tools will be made available to the scientific community so that investigators can perform their own analyses or contact someone to do it for them.

VII. CLOSING REMARKS

Dr. Skirboll assured the Council of its importance to Dr. Collins and speculated that he will continue to consult with CoC regarding his five major areas ripe for scientific exploration. She promised to keep the Council up to date on portfolio analysis and to make Web tools available, and she invited suggestions for future agenda items.

VIII. ADJOURNMENT

Dr. Skirboll adjourned the meeting at 4:20 p.m. on November 16, 2009.

IX. CERTIFICATION

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

Robin I. Kawazoe
Executive Secretary, NIH Council of Councils
Deputy Director, Division of Program Coordination,
Planning, and Strategic Initiatives
Office of the Director
National Institutes of Health