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
November 20–21, 2008

Meeting Minutes

I. WELCOME

Lana Skirboll, Ph.D., Acting Chair, welcomed participants, NIH staff members, and members of the public to the second official meeting of the Council of Councils (CoC). The meeting opened at 8:45 a.m. on Thursday, November 20, 2008, in Building 31, 6th Floor, Room 6, on the NIH Campus, Bethesda, Maryland.

A. Attendance

1) Council Members Present

Acting Chair: LANA SKIRBOLL, Ph.D., Acting Director, DPCPSI, OD, NIH
Executive Secretary: ROBIN KAWAZOE, DPCPSI, OD, NIH
RONALD L. ARENSON, M.D., University of California, San Francisco
ENRIQUETA C. BOND, Ph.D., Burroughs-Wellcome Fund, Research Triangle Park, North Carolina
DONNA BATES BOUCHER, Bates Group, Inc., Denver, Colorado
COLEEN K. CUNNINGHAM, M.D., Duke University Medical Center, Durham, North Carolina
ROBERT M. DICKLER, Association of American Medical Colleges, Washington, District of Columbia
CECILE A. FELDMAN, D.M.D., M.B.A., University of Medicine and Dentistry of New Jersey, Newark, New Jersey
JOSEPH H. GRAZIANO, Ph.D., Columbia University, New York, New York
BEVRA H. HAHN, M.D., University of California, Los Angeles
MARY J.C. HENDRIX, Ph.D., Northwestern University, Chicago, Illinois
DILIP V. JESTE, M.D., University of California, San Diego/VAMC
LENWORTH N. JOHNSON, M.D., University of Missouri-Columbia, Columbia, Missouri
WARREN A. JONES, M.D., F.A.A.F.P., University of Mississippi Medical Center, Jackson, Mississippi
JOSEPH LOSCALZO, M.D., Ph.D., Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts
ORIEN REID, M.S.W., Alzheimer's Disease International and Consumer Connection, Laverock, Pennsylvania
MARTIN ROSENBERG, Ph.D., Promega Corporation, Madison, Wisconsin
RICHARD A. RUDICK, M.D., Cleveland Clinic, Cleveland, Ohio

MARINA E. WOLF, Ph.D., Rosalind Franklin University of Medicine and Science, North Chicago, Illinois

2) Council Members Absent

RICHARD CHABRAN, M.L.S., California Community Technology Policy Group, Los Angeles, California
EDWIN FLORES, Ph.D., J.D., Chalker Flores, LLP, Dallas, Texas
ARTHUR M. KLEINMAN, M.D., Harvard University Medical School, Cambridge, Massachusetts
MARJORIE K. MAU, M.D., University of Hawaii at Manoa, Honolulu, Hawaii
JUANITA L. MERCHANT, M.D., Ph.D., University of Michigan, Ann Arbor, Michigan
SANDRA MILLON-UNDERWOOD, Ph.D., R.N., University of Wisconsin-Milwaukee
DARIA MOCHLY-ROSEN, Ph.D., Stanford University School of Medicine, Stanford, California
SERGIO R. OJEDA, D.V.M., Oregon Health and Science University School of Medicine, Beaverton, Oregon
HAROLD T. SHAPIRO, Ph.D., Princeton University, Princeton, New Jersey
PHYLLIS M. WISE, Ph.D., University of Washington, Seattle, Washington

3) Ad Hoc Representatives Present

JOAN E. FOX, Ph.D., Case Western Reserve University, Cleveland, Ohio
VICTOR M. HESSELBROCK, Ph.D., University of Connecticut Health Center, Farmington, Connecticut
GARY L. WESTBROOK, M.D., Oregon Health and Science University, Portland, Oregon

4) Presenters in Attendance

Faye C. Austin, Ph.D., DPCPSI, OD, NIH
Jeffrey I. Gordon, M.D., Center for Genome Sciences, Washington University
Timothy C. Hays, Ph.D., DPCPSI, OD, NIH
Elizabeth Nabel, M.D., Director, National Heart, Lung, and Blood Institute
Griffin Rodgers, M.D., Director, National Institute for Diabetes and Digestive and Kidney Diseases
James Schuttinga, Ph.D., DPCPSI, OD, NIH
Alan Michelson, M.D., Ph.D., National Heart, Lung, and Blood Institute (NHLBI)
Phil Smith, Ph.D., National Institute for Diabetes and Digestive and Kidney Diseases
Gail Weinmann, M.D., NHLBI
Elizabeth L. Wilder, Ph.D., DPCPSI, OD, NIH

5) Institute and Center (IC) and Office Directors Present

James F. Battey, Jr., M.D., Ph.D., Director, National Institute of Deafness and Other Communication Disorders
Paul Coates, Ph.D., Director, NIH Office of Dietary Supplements
Elizabeth Nabel, M.D., Director, National Heart, Lung, and Blood Institute

Griffin Rodgers, M.D., Director, National Institute for Diabetes and Digestive and Kidney Diseases
Antonio Scarpa, M.D., Ph.D., Director, Center for Scientific Review
Paul A. Sieving, M.D., Ph.D., Director, National Eye Institute
Lawrence A. Tabak, D.D.S., Ph.D., Director, National Institute of Dental and Craniofacial Research; Principal Acting Deputy Director, NIH
Kenneth R. Warren, Ph.D., Director, National Institute on Alcohol Abuse and Alcoholism

6) NIH Staff and Guests

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

B. Meeting Procedures

Ms. Robin Kawazoe reviewed the following:

- Each Council participant has completed and submitted a conflict of interest statement as a Federal requirement for membership on individual IC advisory councils.
- 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*.
- The meeting minutes will be posted on the DPCPSI Web site.

C. Council of Council Meeting Minutes, March 31–April 1, 2008

A motion to approve the minutes was forwarded and seconded. The motion passed unanimously.

II. REPORT OF THE DPCPSI ACTING DIRECTOR

Dr. Skirboll began by acknowledging the many accomplishments of Dr. Elias Zerhouni, who had resigned as NIH Director six weeks before. Dr. Raynard Kington, who had been Deputy Director of NIH, is now serving as Acting Director, and Dr. Lawrence Tabak, in addition to being Director of the National Institute of Dental and Craniofacial Research, is serving as Principal Acting Deputy Director.

Dr. Skirboll then discussed the reorganization that had taken place since the last CoC meeting. She reminded the Council that before the NIH Reform Act of 2006, Dr. Zerhouni already had created the Office of Portfolio Analysis and Strategic Initiatives (OPASI), which was directed by Dr. Alan Krensky and reported directly to the NIH Director. The NIH Reform Act established the Common Fund, the Scientific Management Review Board, and CoC, and it created DPCPSI. The Act was the first omnibus reauthorization in 14 years, and it was viewed by Dr. Zerhouni as an affirmation of NIH's importance and Congress' confidence in NIH.

As stated by the NIH Reform Act, DPCPSI can identify and report on trans-NIH research, allocate Common Fund monies for such research, require proposals to include

milestones and goals for research (if appropriate), and provide appropriate consideration to new investigators. The DPCPSI Director is the NIH Deputy Director for Program Coordination, Planning, and Strategic Initiatives and reports directly to the NIH Director. The Offices of AIDS Research (OAR), Research on Women's Health (ORWH), Behavioral and Social Sciences Research (OBSSR), and Disease Prevention (ODP), which formerly reported directly to the NIH Director, now report to the DPCPSI Director. The Directors of these Offices are now NIH Associate Directors. In addition, the Reform Act created a new office, the Office of Strategic Coordination (OSC). It too reports directly to the DPCPSI Director, and as is the case with the other Offices, its Director is an NIH Associate Director.

With the creation of this new structure, OPASI has been dissolved, but the remaining activities within OPASI will not disappear. The Research, Condition, and Disease Categorization (RCDC) program, portfolio analysis, evaluations, systemic assessments, public health burden, and data/tools functions of OPASI will become staff offices to the NIH Office of the Director (OD),.

Dr. Skirboll concluded by noting that when the Common Fund was first established, it was funded by a percentage of each NIH Institute or Center's (IC) appropriation. Since then, Congress, understanding the need for a Roadmap incubator space, has given the Common Fund a separate appropriation line that is 1.7% of the total NIH budget. Thus, the Common Fund will grow as the NIH grows. In addition, the NIH Reform Act leaves some room for the percentage to change.

In response to questions raised by the Council, Dr. Bob Hammond later distributed organization charts for all of NIH OD.

Discussion Highlights

- Dr. Skirboll clarified that the appropriations for the new staff offices come from the NIH OD appropriation and are not part of the 1.7% allocated to the Common Fund.

- Although OAR, ORWH, OBSSR, and ODP are now under the DPCPSI umbrella, they still report to the NIH Director. In addition, some offices, such as OAR and ORWH, have their own advisory councils, and how these councils will interact with CoC will need to be addressed.

- OSC is directly responsible for managing Roadmap and the Common Fund.

- In response to concerns about changes in emphasis, Dr. Skirboll noted that most of the activities that were part of OPASI are still mandates. Thus, they will continue.

- In response to questions about OPASI, Dr. Skirboll reminded the Council that OPASI was in place before the Reform Act and that the new reorganization had taken place in response to the Act. She also pointed out that the NIH Reform Act of 2006 codifies the Common Fund and the need to identify and report on trans-NIH research. Thus these entities are permanent.

III. NIH WORKING GROUP REPORT: SCIENCE OF SCIENCE MANAGEMENT MEETING

CoC member Lenworth Johnson, M.D. reported on the October 2-3, 2008 meeting on Science of Science management. As framed at the Working Group meeting, science of science management, which aims to accelerate the scientific discovery process and ultimately, to improve public health, includes four tenets:

- Provide evidence-based results for science decision-making, planning, prediction, and policies.

- Identify patterns, pathways, and profiles of science discoveries and scientific careers to identify intervention or tension points that can lead to scientific advancement.

- Build capacity and infrastructure to conduct systematic assessments of science and the science of science management, for improved performance.

- Develop strategies and resources to enable diffusion of the strategies used to assess science management practices.

NIH is only one of several entities that engaged in the science of science management. Others include the National Science Foundation, the Office of Science and Technology Policy, the National Institute of Standards and Technology, and the Department of Energy.

The goal of the Science of Science Management meeting was to identify concepts that can advance assessment strategies, which in turn would be tested by pilot studies and other efforts. Dr. Johnson reported that the meeting participants emphasized the need for a database to assess the current state of knowledge and identify gaps, to examine knowledge generation and see both successful and failed results, to identify and include all stakeholders for knowledge utilization and dissemination, and to assess public health impacts. On the basis of these discussions, Dr. Johnson proposed that DPCPSI support funding for teams to compete in creating a frontier-reaching, instantly updated, scientifically valid, intelligent, and reliable science and medicine database. Such a database should guarantee that users will be within three clicks of the data they wish to evaluate, and it could include a "Just In" section that would post up-to-the-minute contributions of failed and successful research. The database would help NIH place science first, conduct evidence-based science planning, maintain transparency, communicate its plans, and manage change.

Additional information about the Science of Science Management meeting is available at http://nihperformance.nih.gov/ScieceofScienceOverview.htm

Discussion Highlights

- The proposed database would not only require tools to organize and disseminate existing information, but also tools to visualize what kind of information should be

there. Dr. Skirboll pointed out that the staff office of portfolio analysis would focus on these types of tools. She also cited RCDC as the beginning of such a tool, but she also noted that how to analyze data and identify gaps is still poorly understood.

- Discussions of evaluations should include experts from education, as this field has identified ways to assess evaluations.

- CoC members emphasized the need for reliable, up-to-date information at a specific location. This information is needed not only by scientists making discoveries, but by patients trying to manage their own care.

- A second workshop on the science of science management will be held on December 3–4, 2008.

Motion

A motion was proposed and seconded requesting the development of a central database using existing and new tools. This database would represent an amalgamation of evidence-based data and new and emerging information; include a mechanism for verifying the trustworthiness of information; and provide ready access to data, information, and articles for researchers, professionals, patients, and the public. Discussion focused on concerns about the tension between the speed and reliability of information; for example, up-to-the-minute information most likely will not have been vetted. CoC members also discussed the need to know what NIH is already doing.

The Council did not vote on the motion but agreed to discuss it again with Dr. Kington (see below).

IV. RESEARCH, CONDITION, AND DISEASE CATEGORIZATION (RCDC) UPDATE

Dr. Timothy Hays reminded the Council of the NIH goals to increase access about NIH and the research it supports, increase transparency of the information generation and publishing process, maximize impact by leveraging information technologies when possible, standardize reporting across NIH ICs, improve reliability and consistency of reports, establish linkages between disparate pieces of information, and speed up the reporting process. To meet these goals, NIH has established a Web site, http://RePORT.NIH.GOV, which compiles data from several sources and includes:

- The Research Portfolio Online Reporting Tool (RePORT);

- Reports, data, and analyses of NIH research activities;

- The NIH Extramural Data Book;

- The Biennial Report of the NIH Director;

- RCDC; and

- RePORT Expenditures and Results (RePORTER), a new version of the CRISP database.

Data will be available on this site beginning in 2009.

Dr. Hays updated the Council on RCDC, which will go live in 2 months with its initial category data set. RCDC will provide drill-down information on estimated funding for 215 categories historically reported by NIH to Congress and the public. Whereas each IC used to define research topics as they related to the IC's mission, RCDC now provides a standard definition for each category and applies it to all related grants, contracts, and intramural research. In doing so, RCDC provides a uniform process of reporting dollar amounts, increased transparency, a consistent methodology, and a central database and information source. RCDC data also will be available in RePORTER. The first phase of RCDC will include data for FY2008 and estimates for FY2009 and FY2010. A side-by-side category summary comparison of FY2007 data from the old and new methodologies also will be available. This comparison will help the public determine the real changes in funding between FY2007 and FY2008.

RCDC has its challenges. Data inconsistency is a constant challenge, resulting from the integration of several databases, and as expected for any automated system using text-based information, some false positives and negatives might arise from the way authors wrote their descriptions. In addition, some scientific areas are not easily defined or described. The largest challenge, however, will be the discrepancy in numbers and the need to communicate that these changes do not signal a change in priority so much as a change in the methodology used to apply a definition.

RCDC also has its benefits, the largest one being public access to data to determine how NIH estimates its funding for a category. RCDC offers a consistent methodology that NIH can easily describe and demonstrate. Thus its reporting will be reproducible, ultimately leading to improved understanding.

Dr. Hays demonstrated the RCDC tables for the Council. These tables list a disease research area or condition, the FY2007 dollar amounts calculated by the old method, the FY2007 amounts calculated by the new method, and the FY2008 amounts. Users will have the option of exporting this information into an Excel file or other types of formats.

Dr. Hays concluded by noting that many CoC members had participated in the technical review or public review working group. Although DPCPSI had hoped to involve these working groups in testing the system, security issues related to the NIH data set made it difficult to provide access to everyone. Thus the working groups are on hold.

<u>Discussion Highlights</u>

- Any project spanning different topics would be listed in the categories for all related topics. For example, a project focused on lung cancer would be listed as a line under both "lung" and "cancer." Some consider this a form of double-counting; however, NIH discusses funding for every category independent of the other categories.

Therefore, each category is answered as a separate question such as "How much research was spent on Diabetes?" Congress and the Office of Management and Budget understand how NIH counts its projects, and having a project fall into multiple categories is not a new method for NIH. By counting projects this way, NIH answers each question or category to the best of its abilities without confounding the answer by relating it to the other category information reported.

- Even with this way of counting projects, however, NIH might not truly convey how much the diversity of its science plays a role in all areas of biomedical research, including the role of basic research. The inability to truly capture the importance of basic science to all appropriate categories might be especially problematic for areas that are difficult to define or when the results of the basic research are not yet fully understood. ICs already conduct outreach to help the public understand the importance of basic research, but continued communication is needed.

- Although the Council understood the mandate from Congress and the need to roll out RCDC quickly, members emphasized the importance of this data to scientists as well as to Congress and the public.

- DPCPSI is assessing the usability of RCDC from the standpoint of different types of stakeholders. New functions may be added over time with different stakeholders in mind.

- The release of data is dictated by the Department of Health and Human Services (DHHS) and usually occurs with the release of the President's budget. However, with the change in Administrations, data release could be expedited or delayed.

- RCDC represents a large step toward the kind of database discussed by Dr. Johnson and by Dr. Warren Jones.

V. MEASURING THE BURDEN OF DISEASE AND THE CONTRIBUTION OF OBESITY

Dr. James Schuttinga pointed out that illness-associated burden includes premature death; reduced function arising from pain, suffering, or dependence; and economic burden. Obtaining data that capture all these dimensions and are comparable across diseases is difficult. Complete death data is available from death certificates, but assessments of function often depend on surveys and might not capture all its aspects. Disability comprises a major share of health burden, but no one unit captures all disability. Quality-adjusted life years (QALY) or disability-adjusted life-years (DALY) both describe a multidimensional health state and assign scores within a range from perfect health to death. Information on economic burden can be derived from expenditure data of the Centers for Medicare and Medicaid Services (CMS), but costs and expenditures are not allocated to individual diseases and conditions. Indirect costs, for example the lost productivity due to premature death or disability, are alternative measures of health burden. These indicators often are not comparable, detailed studies usually focus only on

one indicator, and the ranking of diseases and conditions varies by each individual dimension of burden. Thus assessments of burden should include all three dimensions.

As is the case with other conditions, the impact of obesity and overweight varies by dimension of burden, as well as by study.

- Two separate JAMA reports estimated about 280,000 to 300,000 deaths due to obesity, poor diet, or inactivity in 1990. This estimate was updated in 2000 to about 385,000 deaths from overweight or obesity, with an additional 15,000 from poor diet and inactivity. The updated estimate was later corrected to about 350,000 deaths from overweight or obesity and 15,000 from poor diet and inactivity. Yet another study, published by Flegal et al., estimated only 111,909 deaths due to obesity but not overweight. Because of these differences in estimates, the impact of obesity on premature death is not clear. A closer look at the study by Flegal et al., who based their estimates on the three waves of the National Health and Nutrition Examination Survey (NHANES), reveals some evidence that the number of deaths due to obesity is declining over time, even as prevalence is increasing.

- Obese or overweight individuals tend to spend more money per capita than individuals of normal weight. In addition, increases in expenditures for obese and overweight persons accounts for 26% of the growth in health care expenditures from 1987 to 2001. One estimate suggests that a 20-year-old will spend an additional $5,340 to $29,460 over his or her remaining lifetime, depending on sex and race, because of obesity. Yet another study estimates that obese 20-year-olds will die 4.5 years earlier and spend 11% less than individuals in a "Healthy Living Cohort."

Dr. Schuttinga noted several challenges for detecting and responding to emerging health threats. These challenges include the time required to verify trends, the need for reliability data on prevalence and burden, public reaction to "crying wolf," and research and development response in terms of additional funding or reprogramming.

Discussion Highlights

- Council members appreciated the difficulty of estimating burden in light of the complexity of most patient populations. Dr. Schuttinga noted that the disparate estimates he presented were not necessarily wrong or the result of mistakes. Rather, they might have changed as more data became available and samples grew larger.

- The data presented by Dr. Schuttinga estimates that 4.7% of premature deaths arise from neuropsychiatric illnesses, whereas other estimates suggest that these illnesses shorten the lifespan by 15 to 20 years. Patients with mental illnesses might have died of other causes, and estimates might change based on how the cause of death is attributed.

- The DALY analysis presented by Dr. Schuttinga was based on U.S. data for 1996. The CDC will release DALY estimates for 2002 in the near future and is expected to continue to develop estimates of DALYs by disease and condition every five to six

years. Dr. Skirboll noted that disease burden is in the eye of the beholder and that the problems facing NIH as it moves aggressively into this area are large. NIH will have to define its role.

VI. NIH OBESITY RESEARCH TASK FORCE

Obesity is associated with many complications in many organ systems, leading to impaired quality of life, considerable morbidity, and premature death. This condition is thus relevant to the missions of many ICs. In 2004, under the direction of Dr. Elias Zerhouni, NIH established the Obesity Research Task Force (ORTF) a trans-NIH collaboration co-chaired by the directors of the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). ORTF now involves 25 of the 27 NIH ICs. Dr. Elizabeth Nabel, NHLBI Director, and Dr. Griffin Rodgers, NIDDK Director, provided the Council with a brief overview of ORTF. Although this initiative parallels efforts within DPCPSI, it is not involved with the Division.

At the time ORTF was established, the NHLBI and NIDDK Directors developed and published a strategic plan (http://obesityresearch.nih.gov) framed around basic science, clinical investigations, epidemiologic studies, behavioral and environmental studies, economic research, translational research projects, and education and outreach programs. When Drs. Nabel and Rodgers became the Directors of these Institutes, they conducted an evaluation of ORTF, based on the strategic plan, and they are now in the process of updating this plan, with the goal that it serve as a living document.

Drs. Nabel and Rodgers highlighted efforts in four domains:

- **Identifying factors that cause or contribute to obesity.** In 2005 ORTF held a workshop on the intrauterine environment and long-term consequences for obesity and metabolic disease. This workshop led to a funding opportunity announcement (FOA) that funded both animal and human studies. ORTF also has recruited new obesity researchers to explore the economics of diet, activity, and energy balance and fostered collaborations between these researchers and those from more traditional disciplines of cancer and other chronic diseases. Other efforts include an NHANES substudy on the percentage of U.S. adults meeting recommendations for physical activity, an FOA for studies of geographic and contextual influences on energy balance-related health behaviors, research on obesity and other side effects of psychotropic medications, and neuroimaging studies on the role of the brain in appetite and energy storage and expenditure.

- **Enabling measurement and analysis of diet, physical activity, and other contributors to obesity.** ORTF issued an FOA for studies to improve measures of diet and physical activity, particularly measures based on genes and environment. Two studies have been funded to develop technology-assisted dietary assessments and physical activity measures. Ongoing studies include the integration of heart rate and movement to improve physical activity assessments, development of a tool to measure food availability in the home, and physical activity assessments based on

variability in accelerometer counts. ORTF also is funding bioengineering efforts, some in collaboration with the National Science Foundation, and the task force is interested in supporting small businesses to further develop these measures. The task force also has issued an FOA to develop innovative statistical and computational methodologies for design and analysis of multilevel studies on childhood obesity.

- **Developing, testing, and evaluating intervention strategies.** ORTF issued FOAs to support studies of site-specific approaches for prevention or management of childhood obesity, as well as studies of the prevention and treatment of pediatric obesity in a primary-care setting. Dr. Rodgers also discussed two studies that were ongoing before the task force was established: the Look AHEAD Study, a multi-center clinical trial examining the long-term effects of an intensive lifestyle intervention versus a diabetes support and education program (the Diabetes Prevention Program) in more than 5,000 overweight or obese patients with type 2 diabetes; and the Diabetes Prevention Program Outcomes Study, an ongoing follow-up study to examine the durability of the program in preventing or delaying diabetes and its long-term complications. Ancillary studies are ongoing for both these studies. Other ORTF efforts include intramural community projects such as the Trans-NIH Metabolic Clinical Research Unit, which provides specialized, state-of-the-art facilities for comprehensive and collaborative research on factors driving the obesity epidemic, and a basic research project on WAGR syndrome, which arises from a homozygous deletion of brain-derived neurotrophic factor, a protein involved in body-weight regulation.

- **Disseminating research results to health care professionals, patients, and the public.** ORTF has begun to develop outreach programs and partnerships to capitalize on research findings and disseminate them to the community. Efforts include a national survey of energy balance-related care among primary care physicians; an evidence-based update of clinical guidelines on obesity in adults, with an anticipated release date of 2010; and the *We Can!* program, an evidence-based program to help children and families maintain a healthy weight. This program is ongoing in 920 community sites in 50 states, the District of Columbia, Puerto Rico, the Mariana Islands, and nine other countries.

Discussion Highlights

- ORTF benefits from cross-talk among ICs. For example, depression can be both a cause and a consequence of obesity, and project officers from NHLBI and NIDDK might work with those from the National Institute of Mental Health (NIMH) in incorporating depression into ORTF assessments.

- ORTF is working with public relations, advertising, and social-marketing groups to conduct marketing surveys, develop materials, and manage knowledge dissemination. The task force has not, however, established an integrated communication to pitch to investigators.

- NCI has established a research model to identify environmental factors that might contribute to cancer, and this model can now be used to examine data, for example, on urban communities that have access to supermarkets versus those that do not. Studies based on this data could ultimately be used to inform policymakers.

- Each participating IC has its own appropriated budget and establishes its own strategic priorities. NHLBI welcomes studies of primary prevention or intervention strategies in childhood obesity, and it also generates its own initiatives.

- During their presentation, Drs. Nabel and Rodgers described several devices under development. However, this is still a new area of study, and these devices are not yet ready for commercial development.

- NHLBI has pediatric guidelines on cardiovascular risk factors, including information on diabetes.

- ORTF benefits from the passion and commitment of its participants to the public health need. People involved in ORTF also look for opportunities to form partnerships.

VII. MICROBIOME

A. Human Microbiome Project

Dr. Rodgers briefly discussed the NIH Human Microbiome Project (HMP), a Roadmap initiative aimed at characterizing microbial communities that inhabit the human body and determining how intra- and interpersonal variations in our microbial ecology affect health and disease predisposition. The initiative provides resources needed to support an interdisciplinary program The HMP is funded at $125 million over 5 years.

B. Microbiome

Dr. Jeffrey Gordon provided an overview of HMP. He noted that human beings are composed of cells representing all three domains of the tree of life, and that our adult bodies harbor 10 times more microbial cells than human cells, with the largest collection of microbes inhabiting our distal gut. The microbiome refers to the aggregate genomes of all the microbial species represented in our various microbial communities.

The HMP is seeking to find answers to a number of fundamental questions. For example, how much diversity is there in our microbial communities; is there a ‘core’ group of microbial species and genes that we all share, or most of us share, in a given body habitat? Should differences in our microbial communities (microbiota) and microbiomes be viewed as features of our biology that are profoundly affected by both our *Homo sapiens* genotypes and by our individual environmental exposures? How are human body habitat-associated microbiomes evolving within and between individuals, over time, as a function of our changing diets, lifestyles, and biosphere? Is there a dimension of human evolution that is occurring rapidly and not at the level of our human DNA, but rather at

the level of our microbial DNA? If so, can this "micro-evolution" be correlated with changes in our human physiology, and with worldwide alterations in our risk for certain common or uncommon diseases? Can we best capture the significance of these changes in our microbial ecology by studying people living in countries that are undergoing dramatic transformations in their cultural traditions and technologies?

Analyzing the microbiota through culture-based methods is hampered by a lack of sufficient knowledge regarding the normal metabolic milieu in which microbial communities exist. Therefore, only a small fraction of community members can be recovered by culture using existing technology. However, the 16S rRNA gene can be used for so-called "culture-independent" surveys of microbial community composition. This gene is present in all members of the domain Bacteria and Archaea. Moreover, it contains fast and more slowly evolving regions. Therefore, the polymerase chain reaction (PCR) can be used to amplify 16S rRNA genes present in DNA that has been isolated from a microbiota harvested directly from its environment, without culture. PCR primers are designed that recognize conserved regions of the 16S rRNA gene, but flanking the gene's variable regions. The resulting PCR products are sequenced using traditional capillary or next generation highly parallel DNA sequencers. Alignments of the resulting gene sequences can be used to resolve phylogenetic relationships at different depths; taxa are operationally defined based on the degree of sequence similarity they share among their 16S rRNA genes; for example, members of a species are customarily said to share ≥97% identity in their16S rRNA gene sequences.

Dr. Gordon discussed several examples of how these methods, combined with new computational tools for defining the degree of similarity between communities, have been applied to humans at early phases of the HMP. These examples include:

- A study of the influence of gender, handedness, and washing on the diversity of bacteria present on the hands of college students;

- Studies of the vaginal microbiota;

- A study of the biogeography of microbial communities in the mouth;

- A study of the effects of orally administering an antibiotic on the gut microbial community of a few healthy adults.

Dr. Gordon also described recent studies from his group examining the dynamic interrelationships between diet, gut microbial ecology, and energy balance. Germ-free mice are leaner than their conventionally-raised counterparts, even though germ-free mice consume more chow. Studies of conventionally raised mice that are obese because they were homozygous for a null mutation of the leptin gene, or because they consumed a Western diet, revealed that obesity is associated with changes in the proportional representation of major bacterial phyla in the gut and alterations in the gut microbiome. Transplantation of a gut microbiota from obese mice to germ-free mice produces a greater increase in adiposity in recipients than does transplantation of a gut microbiota from lean donors. He subsequently outlined findings from studies of the fecal

microbiota/microbiomes of adult female identical (monozygotic) and fraternal (dizygotic) twins who were concordant for obesity or leanness, and their mothers. The results showed that: (i) family members share significantly more bacterial species than unrelated individuals; (ii) the degree of similarity of the gut communities of monozygotic and dizygotic twin pairs was not significantly different, highlighting the important role of early environmental exposures in defining gut microbial community composition; (iii) there was not a single abundant (defined as representing >0.5% of the microbial population) gut bacterial species shared among all 154 individuals surveyed; (iv) however, there was an identifiable set of microbial genes that was shared by all surveyed individuals; these genes encode key metabolic functions; these results indicate that different assemblages of gut bacterial species can provide similar functions (i.e., the "core" is not at the level of species but rather at the level of microbial genes); (v) obese monozygotic twins contain gut microbiomes enriched for at least 300 genes involved in a number of aspects of nutrient processing.

Defining the composition and operations of human-associated microbial communities demands careful selection of reference controls, analyses that go beyond DNA level characterization, plus identification of the basic principles that govern assembly and adaptations of communities; these principles need to be gleaned from experimental work conducted in model organisms such as gnotobiotic animals. Among the expected outcomes of this work are a new and deeper understanding of human nutrition; increased understanding of the impact of our evolving cultures, lifestyles, and technology on our human biology; new definitions of health; and the potential for engineering our microbial community metabolism in ways that enhance wellbeing. Related outcomes of the HMP may be a new set of beneficial "natural" microbial products that represent new components of our 21st century pharmacopoeia, or newly identified functions for human genes found to be manipulated by our microbial communities; these human genes may, in turn, become targets for new classes of drugs. The HMP is expected to produce many technological spin-offs, including new diagnostics and therapeutics; as such it may spawn a number of SBIR grants. In addition, the HMP is taking place at a fascinating time of "democratization" of genome sequencing; this democratization is allowing smaller groups direct access to next generation sequencers so that they undertake formerly daunting projects while at the same time using these instruments to develop new and innovative experimental and computational approaches. Finally, as a roadmap project, HMP can be strategically and creatively used to spawn new educational programs for the public and for students; the latter would allow students to operate at the interface of formerly discrete disciplines.

Discussion Highlights

- Mono- and dizygotic twins represent a very attractive study paradigm during the early stages of the HMP, as it seeks to dissect the relative contributions of host genotype and environment on our microbial ecology. Twins experience common environmental exposures, particularly during the early post-natal period. Twins who are discordant for a physiologic or pathophysiologic state offer powerful sets of controls (each affected co-twin can serve as his or her own control over time, or with treatment, while the unaffected co-twin serves as another control).

- More studies are needed to understand how microbial communities assemble, how they maintain their robustness (adapt to perturbations), and how they shape their surrounding habitats. Microbial communities are capable of remarkable biotransformations. However, the nature of their metabolism and the implications for human health are underexplored. For example, what is the role of a gut microbial community in defining the bioavailability of orally administered drugs or the fate of ingested potential or known carcinogens?

- Microbiome analysis is fraught with a large number of confounding factors and thus very challenging. It should be approached in a systematic way. Potential variables to explore include the impact of the innate and adaptive immune systems, nutritional status, familial relationships (including marriage), and various pharmacologic agents (antibiotics, immunosuppressives, chemotherapy).

VIII. HIGH-RISK, HIGH-REWARD RESEARCH DEMONSTRATION PROJECT

In response to the NIH Reform Act of 2006, NIH implemented two demonstration projects:

- Bridging the Sciences: grants at the interface between the biological, behavioral, and social sciences and the physical, chemical, mathematical and computational sciences.

- High-Risk, High-Reward (HRHR) Research: grants, contracts, or other transactions for high-impact, cutting-edge research that fosters scientific creativity and increases fundamental biological understanding leading to the prevention, diagnosis, and treatment of diseases and disorders.

The implementation of these projects involved the creation of Legislative Implementation Action Plans (LIAPs). For each demonstration project, the NIH created a Demonstration Oversight Group, which includes senior NIH officials and IC directors to review current NIH activities in these areas, and an Implementation Group to assist each Oversight Group.

Dr. Faye Austin focused her presentation on the HRHR demonstration project and the specific goals of its LIAP:

- **Define standards for evaluation and reporting.** For the purpose of this project, the HRHR Demonstration Oversight Groups has defined HRHR research as "research with an inherent high degree of uncertainty and the capability to produce a major impact on important problems in biomedical/behavioral research." The Oversight and Implementation Groups have defined specific questions for this analysis, including how effective the NIH has been in supporting HRHR research, whether new Roadmap programs have been successful in promoting HRHR research, whether other IC programs have been used effectively to encourage or support HRHR research, and whether there are gaps or opportunities indicating the need for HRHR research demonstration projects. Data-driven analysis is under way to address perceptions that NIH is too conservative and that risky projects do not get funded. In

addition, the Groups have developed a strategy for data collection and analysis, which includes establishing a "best-case baseline" by analyzing applications submitted for Funding Opportunity Announcements (FOAs) that specifically encouraged HRHR research; a retroactive "prospective" analysis of reviewer comments and summary statements; and the use of "best-case" data to develop a text-mining tool unsolicited HRHR applications.

- **Conduct portfolio analysis to identify gaps and opportunities.** The Implementation Group's analysis shows that HRHR applications are submitted when specifically encouraged by HRHR FOAs and that the success rate for HRHR applications is almost three times higher than that for non-HRHR applications. For the HRHR FOAs analyzed, there was no apparent benefit from special review groups, special review criteria, or set-asides of funds. HRHR program announcements solicit and fund more applications total than do HRHR requests for applications, although the proportion of successful applications is the same for both types of announcements. The main determinant for the actual number of HRHR grants funded is the number of HRHR applications submitted. The Implementation Group concluded that when the potential payoff of a project is high and the application is clearly written, the system is not risk averse. The Oversight and Implementation Groups indicated that the potential impact of a project must be considered first, even though the term "High-Risk, High Reward" and the current definition of HRHR mentions risk first.

- **Identify and develop potential initiatives.** The Oversight and Implementation Groups reviewed current HRHR programs, such as the NIH Director's Pioneer and New Innovator awards, as well as IC programs such as EUREKA (Exceptional Unconventional Research Enabling Knowledge Acceleration), CEBRA (Cutting Edge Basic Research Awards), and Quantum. Success of HRHR programs in supporting high-risk high-reward research needs to be measured by actual funding to support HRHR projects and not by the resulting scientific outcomes. The Groups will continue to review these programs and develop recommendations as needed.

- **Seek to facilitate partnerships between public and private entities and coordinate, when appropriate, with the Foundation for the NIH.** Work has not yet begun in this area.

The HRHR LIAP also will be used to generate a report to Congress by September 2009.

Discussion Highlights

- Council members appreciated the amount of work that had been done, but some remained skeptical because applications were classified as high impact based on a review of summary statements. Investigators who perceive that HRHR applications fare poorly in study sections might not accept this method of classification. DPCPSI is aware of a general skepticism and will continue to identify ways to address it.

- The HRHR Oversight and Implementation Groups should be careful in assessing how risk is assigned, as definitions used by reviewers might differ from the definition the Groups use. One Council member suggested convening a group of venture capitalists and asking how they identify projects as HRHR.

- From an industry perspective, high risk involves a high likelihood of failure. As DPCPSI moves forward, managing failure and defining when to stop a study will become critical. NIH will have to determine how much risk it is willing to accept and consider how to distinguish between renewing good but risky projects and throwing money away.

- Historically, NIH has been conservative with respect to new investigators or proposals with little or no preliminary data. Council members expressed concern that applications that have potential for high reward still might not be funded because of this lack of data. The R21 mechanism was intended not to require preliminary data, but it has become more like a small R01 in its use in recent years. Dr. Austin noted that programs such as EUREKA are designed to break this mindset.

- NIH has not compared the success of HRHR applications versus low-risk, high-reward applications.

IX. REMARKS FROM THE ACTING DIRECTOR, NIH

Dr. Raynard Kington began by acknowledging the importance of DPCPSI and the efforts of Dr. Skirboll and Dr. Lawrence Tabak, Director of the National Institute of Dental and Craniofacial Research and Principal Acting Deputy Director of NIH.

Awards

NIH grantees Martin Chalfie, Ph.D., of Columbia University, and Roger Y. Tsien, Ph.D., of the University of California, San Diego, shared the Nobel Prize in chemistry with former NIH grantee Osamu Shimonura, Ph.D., of the Marine Biology Laboratory in Woods Hole, Massachusetts. These investigators were honored for discovering green fluorescent protein and developing it as a tool for observing processes that until then had been invisible. Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, has received the Presidential Medal of Freedom and was asked to address the United Nations General Assembly at its recent meeting on AIDS.

Personnel

Several leadership changes have taken place. On October 31, 2008, Dr. Ting-Kai Li resigned as Director of the National Institute on Alcohol Abuse and Alcoholism and retired from Federal service. Dr. Kenneth Warren is serving as Acting Director. In August 2008, Dr. Francis Collins resigned as Director of the National Human Genome Research Institute to pursue other professional opportunities. Dr. Alan Guttmacher is serving as Acting Director. Dr. Norka Ruiz-Bravo has stepped down as Director of the Office of Extramural Research, after 5 years of service. She will continue as a special

advisor. Dr. Sally Rockey is serving as Acting Director. These vacancies most likely will not be filled until the new NIH Director is appointed.

Legislation

Several hearings were held during the 110th Congress. At the last one, on November 13, 2008, Dr. Kington testified regarding the role of biomedical research as part of an economic stimulus package. Because NIH has a system primed to act quickly, some argued that it could quickly distribute funds to institutions that are major employers in their communities in the short term and help the Nation restore its investment in biomedical research in the long term. NIH most likely will not be included in the first economic stimulus package but might be included in subsequent packages. Dr. Kington acknowledged Dr. Zerhouni's efforts in helping Congress to consider NIH as an investment and not just a cost.

Dr. Kington also reported that more than 200 bills had been proposed but ran counter to the NIH Reform Act and the overall mission of the agency, and that the House passed a bill related to the Small Business Innovation Research (SBIR) and Technology Transfer (SBTTR) programs. NIH does not support legislature that is specifically targeted and proscriptive, nor does it support increasing the set-aside for SBIR/SBTTR.

NIH is implementing Title VIII of the Food and Drug Administration (FDA) Amendment Act, which mandates expansion of ClinicalTrials.gov, expansion of the number of trials required to be listed, and inclusion of results information for treatments and devices. NIH is working with FDA and the National Library of Medicine (NLM) to respond to these requirements.

Dr. Kington reported that NIH also is working with transition teams for the incoming Obama Administration.

Appropriations

NIH is operating from a continuing resolution passed September 30, 2008. This continuing resolution funds Government at the previous fiscal year levels until March 2009. It is expected that Congress will quickly focus on appropriations at the beginning of its next session. Four appropriations actions will be considered: FY2008, FY2009, FY2010, and a potential economic stimulus package.

Financial Conflicts of Interest

Extramural financial conflicts of interest continue to be a significant area of interest. Senator Chuck Grassley (R-IA) has spoken with NIH, other Federal Government agencies, and universities about allegations that some individuals funded by NIH have received undisclosed financial support from or have undisclosed financial interests in the private sector. Dr. Kington pointed out that NIH has responded aggressively to these concerns, but he also noted the need for NIH to rethink existing regulations governing they way grantees manage their financial conflicts. NIH will issue a request for information from the community.

NIH Reform Act Activities

Dr. Skirboll is overseeing a new biennial report, required by the NIH Reform Act that illustrates the range of research supported by NIH. CoC members received copies of the report on compact disc. This biennial report consolidates several individual reports on specific topics. Also in response to the Reform Act, a Scientific Management Review Board was chartered in August 2007, with the broad charge of assessing how the structure and operation of NIH affects its ability to achieve its mission. The legislation requires that this board, which consists of nine IC directors and eleven members from outside NIH, conduct a comprehensive review of NIH structure every 7 years. The first board meeting was held in January 2008.

Peer Review

NIH has conducted a comprehensive assessment of its peer review system and concluded that although the system has worked overall, some areas, such as committee-driven review, require improvement. In addition, assessing HRHR research remains a challenge. NIH is looking at new ways to engage reviewers, improve the quality and transparency of review, assure balance and fair review across scientific fields and career stages, and institutionalize a continuous assessment of how the system is performing. NIH is implementing several changes, including a new scoring system; decreasing the number of allowed resubmits from two to one and programmatic shifts to fund more first submissions; a new, more transparent structure for information given back to applicants; and an ongoing system to survey various constituencies and ascertain how changes are working.

Undiagnosed Diseases Program

In May 2008, NIH launched a new program that would provide opportunities for physicians and health providers to refer patients with puzzling but undiagnosed conditions to NIH. The agency will screen and evaluate these patients and, if appropriate, place them on protocols to diagnose unusual or rare diseases or unusual presentations of common diseases. NIH has received a large number of applications and is thinking about how to institutionalize the program and involve extramural scientists.

Discussion Highlights

- Dr. Kington noted that the Undiagnosed Diseases program most likely includes children. He also discussed the challenges of establishing an infrastructure to review records and define which patients are considered undiagnosed.

- Council members expressed concern that the NIH conflict-of-interest rules went too far and were pejorative to hiring and other activities. They appreciated NIH rethinking the rules, but they also worried about burdening the system with more paperwork and regulations. Dr. Kington agreed that the first version of the NIH rules went too far, but he also pointed out that Federal employees are different and that NIH must assure the public that it is an independent entity. He also noted changes in

the magnitude and complexity of relationships with industry and the need for awareness, across institutions, of the dangers inherent in losing public trust.

- In response to mentions of the motion made earlier regarding a comprehensive database, Dr. Kington noted that the NIH Web site is already the most used site for reliable public health information, that NLM offers a large amount of user-friendly information, that the new discussions of the science of science management include ways to find new knowledge and connect areas of science that are not obviously related, and that RCDC and other activities represent small steps in analyzing the NIH portfolio and understanding how the scientific knowledge base is changing. In addition, NIH has discussed ways to improve its job and reduce the amount of time between the discovery and application of new knowledge. Although Dr. Kington did not think such a motion was necessary, he acknowledged that the motion was consistent with goals the NIH has been trying to reach for some time.

- Dr. Kington noted that NIH will implement pilot projects exploring an editorial board approach to peer review, in which an application is first reviewed and scored by a small committee with expertise in the areas addressed by that application. Dr. Kington also noted a tension between acknowledging expertise and having a big-picture view that is open to new approaches.

- Dr. Kington noted lengthy discussions of ways for NIH to encourage institutions to change their levels of commitment to and investment in new investigators. Although many business models exist, some of which do offer this type of encouragement, NIH leadership acknowledge that emphasizing one structure would have dramatic effects depending on the institution, its resources, and its operating model.

- Dr. Kington clarified that mechanisms to smooth the transition to funding more at first submission varied across ICs and that ICs are carefully exploring their options. Each IC will have to use more of its discretionary funds to pull those applications out of the queue.

- Although the NIH offers a wealth of information on its Web site, some people still do not have ready access to a computer or the Internet. Although members of the public are becoming more sophisticated consumers of information, the traditional media are cutting back on investments in people dedicated to and specializing in health information.

X. TRANSFORMATIVE R01 PROGRAM (T-R01)

Dr. Elizabeth Wilder reminded the Council that fostering transformation through investigator-initiated projects has been a key goal of the NIH Roadmap HRHR Program and that the Pioneer awards and New Innovator awards represent the first two programs of this type in Roadmap. The Pioneer Award supports individual scientists of exceptional creativity who propose pioneering and possibly transformative approaches to challenges in biomedical and behavioral research, and to be considered pioneering, the proposed ideas must be substantially different from those already pursued. The New Innovator

Award represents an expansion of HRHR efforts to new investigators, defined as those within 10 years of having received their doctorate. Dr. Wilder reported that in 2009, competition for each program will occur in two stages, under two separate FOAs. The first will request pre-applications, which will be assessed by external reviewers, and the second will invite investigators with the most outstanding pre-applications to undergo a limited competition.

At the time the Pioneer awards were established, there was a call to identify highly transformative projects. Although the idea was not pursued at the time, the idea kept resurfacing in a Fostering Innovations workshop in December 2007, in efforts to enhance peer review, and in the HRHR Demonstration Oversight Group. The Transformative R01 (T-R01) Program was established to encourage projects:

- With potential to create or overturn fundamental paradigms;
- That are innovative, inventive, original, and/or unconventional (that is, risky); and
- That will have a major impact on biomedical or behavioral research.

The program will be open to all scientific fields of interest to NIH, and budgetary flexibility will allow support of projects of varying complexity. Twenty-five million dollars has been allotted for the program in 2009, with no individual cap. Whereas the Pioneer and New Innovator awards seek to identify and support individuals, the T-R01 program seeks to foster projects, with minimal oversight by NIH. Flexible research authority will be used to support high-risk projects to reach a defined goal, though NIH will maintain control to ensure the project meets milestones toward that goal.

Although the T-R01 program is open to all areas, the strategic planning process highlighted areas of particular need:

- Understanding and facilitating human behavior change.
- Complex three-dimensional tissue models.
- Functional variation in mitochondria in disease.
- Transitions from acute to chronic pain.
- Formulation of novel protein-capture reagents.
- Providing an evidence base for pharmacogenomics.

Dr. Wilder emphasized, however, that these are not the only areas that will be funded.

To raise awareness of the T-R01 program, NIH has engaged communities engaged in transformative research and fostered brainstorming sessions to encourage communities to consider how fields can be transformed.

The program is for extramural investigators only, and multiple principal investigators are acceptable. Applications will be due January 29, 2009. Peer review will take place in spring 2009, and CoC will provide a second-level review in summer 2009 to ensure that initial reviews were conducted with appropriate expertise and lack of conflict. Awards will be made in September 2009. DPCPSI considers the T-R01 program to be a pilot program, and the FOA will be re-issued every year for 5 years. Whereas the Pioneer and New Innovator award programs are managed through NIH OD, T-R01 awards will be managed by the IC most scientifically relevant to their projects. ICs will work with NIH OD to develop funding plans for the proposals, and the NIH Director will make the final selection.

Dr. Antonio Scarpa, Director of the Center for Scientific Review (CSR), added that T-R01 applications will undergo an "editorial board review," in which a small study section of distinguished, broad-science reviewers will triage applications based on innovation and potential scientific transformation. Specific science will be assessed by the appropriate reviewers, and "editors" will make the final ranking.

Dr. Scarpa explained that changes in the peer-review process were driven by flattened NIH budgets, the growing number of applications submitted, reviewer load, and constraints on the CSR budget. CSR has generated annual savings in reviewer expenses by purchasing non-renewable tickets that allow only one change, by cutting the number of reviewers by 3,000, by using electronic platforms for 15% of reviews, and by holding one review meeting a year on the West Coast.

CSR has worked to enhance peer review by reorganizing based on scientific area and by recruiting new scientific staff. The Center also has revised its study section guidelines and is improving study section alignment and performance. The review cycle has been shortened to provide applications a review and score within 3 months of submission, thus allowing almost immediate resubmissions if needed. Deadlines have been made more flexible, and A2 applications have been abolished. CSR is also working to improve the quality and transparency of peer review by shortening summary statements and having them follow a template for each criterion (February 2009), by changing the rating system, and by shortening applications and aligning them with review criteria (February 2010). Finally, CSR is recruiting the best reviewers and reducing the need for *ad hoc* reviewers. In addition to holding a West Coast meeting and implementing new review platforms, CSR is developing a national registry of volunteer reviewers, providing both tangible rewards and flexible time for reviewers, and improving training.

Training of study section chairs has begun. One hundred, fifty new study section chairs have been appointed and will undergo five training meetings in January 2009. A second set of five meetings will be held in July 2009 for 150 chairs appointed in June. The training program will share data, explain the new changes and their significance, share best practices, answer questions and address concerns, and make study section chairs more effective stakeholders.

<u>Discussion Highlights</u>

- Council members pointed out that little funding goes to investigators from the South and that these investigators are not well represented on review committees. CSR is aware of the problem and working to address it.

- Overall, success of the T-R01 program will be judged on its ability to achieve transformative results. However, Dr. Wilder acknowledged that this type of judgment will be difficult midstream and even at the end of the 5-year period. DPCPSI does not anticipate that each individual project will be renewed from within the Common Fund, and depending on the project's size, it might not be supported by an IC. However, normally sized projects might be able to recompete in traditional IC processes. DPCPSI is still trying to determine what an acceptable failure rate is.

- Dr. Scarpa noted that budget constraints have not had an impact on the quality of reviews.

- Dr. Wilder clarified that at the second-level review, CoC is not intended to rescore applications. Rather, the Council will ensure that the approach and the application of scientific expertise were fair. DPCPSI will brief CoC on the review process before next summer's review.

- Although Council members expressed excitement about the HRHR pilot programs, they cautioned that NIH should be careful not to give the impression that R01 projects in general represent boring, incremental science. Dr. Skirboll emphasized that R01-supported basic research remains the core of the NIH portfolio and that the overall system is still good. However, this core is conservative, and NIH wants to devote a small percentage of its budget to riskier, potentially transformative approaches.

XI. PROPOSED NIH ROADMAP INITIATIVE CONCEPTS

A. Review of Process and Criteria

To prepare the Council for this round of concept clearances, Dr. Wilder reviewed the overall process and criteria for Common Fund projects. She reminded the Council that public clearance of concepts provides assurance that funds are directed toward the most pressing needs of the community. Concept clearance occurs differently across ICs, but IC Advisory Council discussion is advisory to the IC Director and provides one source of input for priority setting.

DPCPSI is still determining the most productive approach to concept clearance for the Common Fund. In the model employed at this meeting, concepts would be presented for early discussion to help shape concepts as program proposals were developed, and CoC discussion would be expected to help the DPCPSI Director determine which concepts might move forward for further development and for discussion with the NIH leadership. Although the proposals at today's meeting were still in early stages, Dr. Wilder pointed out that some early analysis was done and summarized for the Council in their pre-meeting documents. This analysis included portfolio analysis through RCDC, literature

reviews and synopses, non-NIH funding, and gap analysis, as well as public input from requests for information and external panels.

Roadmap programs must meet the following criteria:

- The initiative should be truly transforming, affecting how research is done over the next decade. This means that the initiative creates new tools or services or generates new paradigms of knowledge.

- Outcomes from the initiative should synergistically promote and advance the individual missions of the ICs to benefit health.

- The initiative should require participation from NIH as a whole, or at least from more than one IC. Broad relevance is value added.

- The initiative must be something no other entity is likely or able to do, and there must be a public health benefit to having research results in the public domain. If another entity is addressing the issue or is likely to, the Roadmap initiative must describe a niche that is likely to be unique to NIH interests.

Discussion Highlights

- Dr. Wilder noted that although a Roadmap initiative must represent something no other entity is likely to do, NIH might collaborate with other entities to implement it. One of the first Roadmap initiatives was the establishment of an Office of Public-Private Partnerships. NIH also is interested in collaborating with agencies across DHHS.

- If concept clearance for Roadmap initiatives continues to occur at early stages, CoC could identify potential partners for initiatives.

B. Clinical IMPACT Awards Program

In 2005, Senator Joseph Lieberman (I-CT) called for the establishment of a Center for Cures to speed the development of cures for human illness and injury. This call was resurrected again in 2008 by Harold Ford, Jr., and Al From. Katie Hood, chief executive officer of the Michael J. Fox Foundation for Parkinson's Research, echoed these sentiments, questioning the good of funding the "greatest discovery engine" if that investment is not converted into improvements in human health. The bulk of NIH funding supports basic discovery research, and although it also supports studies in late-stage clinical research, that type of investment is dwarfed by the pharmaceutical industry's investment at the same stage. The intermediate stages, including early and late therapeutic discovery research, are not adequately addressed by either NIH or the pharmaceutical industry. Some NIH programs, such as the Molecular Library Screening Center Network and the Rapid Access to Interventional Development, address particular steps, but overall the intermediate stages represent a "valley" in translating discoveries to impacts on human health.

The proposed Clinical IMPACT Awards Program aims to catalyze translation of discovery to a real impact on human disease. It will provide an environment for transformation, as well as incentives that encourage risk and overcome the fear of failure. The Clinical IMPACT Awards Program includes the following principles:

- A major effort by principal investigators, developing collaborative teams of flexible make-up.

- The potential for stable, long-term funding, 10 years or more without study section peer review.

- Interim reviews based on measurable milestones proposed by the applicants.

- Significant funding at a level commensurate with the challenge.

During his presentation, Dr. Phil Smith of NIDDK discussed several possible models for Clinical IMPACT projects. For example, he cited a paper showing that adult stem cells could be driven to be pluripotent, obviating the need for embryonic stem cells. This opens a new field of research that is advancing at a rapid pace, would make patient-specific cells possible to obtain, and would increase the use of autologous transplants and eliminate the risk for transplant rejection. However, there are still some challenges to overcome. Some transcription factors used to induce pluripotency are also oncogenes, and others are introduced virally. The long-term potential and survival of induced pluripotent stem cells are not known, and how these cells compare with embryonic stem cells is poorly understood. Yet a recent study in patients with diabetes revealed a way to obviate the need for two transcription factors, and another suggested the utility of induced pluripotent cells in addressing amyotrophic lateral sclerosis.

Dr. Smith concluded his presentation by highlighting factors to be used in setting priorities for Clinical IMPACT projects:

- Potential for significant health benefit;

- Ability to identify specific translational steps that will lead to measurable translational advances;

- The existence of scientific teams, clinical samples, and infrastructure to carry out specific translational steps;

- Definitive points at which progress can be evaluated through milestones; and

- The importance of NIH funding for the work to advance.

<u>Discussion Highlights</u>

- The proposed program classifies as a Roadmap initiative because it is intended to develop a laboratory for testing ways to bridge translational gaps.

- Although the presentation focused on procedures and cure, IMPACT projects also could focus on prevention.

- Dr. Smith clarified that the proposed program is intended to give investigative teams an opportunity to determine whether they can have a significant impact on disease, not necessarily to promise a cure.

- Dr. Smith emphasized that the proposed program will encourage the development of flexible teams that can change as new expertise is needed.

- Council members commented that the schema for the Clinical IMPACT Awards Program could provide a context for the public to understand the importance of basic science, the intermediate steps that fall into the "valley," and the need for funding at all steps. However, this schema also could constrain NIH by forcing it to classify all its activities in terms of a potential cure.

- Because efforts toward a cure eventually include clinical work, DPCPSI should consider whether clinical work should be a requirement of the proposed program.

- With respect to review, NIH envisions a process similar to that used for the T-R01, where a committee looks not so much at detail as at the plan and the team. The review committee would represent broad interests and perhaps include venture capitalists.

- Council members suggested that the program be structured in a way where initial groundwork for Clinical IMPACT projects is accomplished through the T-R01 program. Dr. Smith thought requiring a T-R01 might be problematic, but he agreed with the need for applicants to lay out the groundwork as they discuss why a proposal could succeed.

- NIH can explore lessons learned by talking with private disease foundations that have attempted to form partnerships with venture philanthropy.

- Because developing a 10-year strategy will take some time, NIH might want to announce the application process far ahead of the receipt date.

C. Mechanism-associated Phenotypes for Genetic Analysis (MAPGen)

Dr. Gail Weinmann noted that, although diseases coexist, the research community tends to focus on organ-based manifestations of disease. In so doing, researchers lose a focus on the shared underlying mechanisms of different diseases, making it difficult to leverage research across all ICs. Advances also are hampered by inadequate and sometimes inaccurate phenotypes for genotype associations. Thus opportunities for drug development are missed because shared mechanisms are poorly understood.

The Mechanism-associated Phenotypes for Genetic Analyses (MAPGen) initiative would be used to define human diseases based on underlying pathophysiology and redefine disease phenotypes according to shared mechanisms. The initiative would comprise three

components. Program 1 would involve hypothesis generation using existing datasets, Program 2 would involve hypothesis testing using existing datasets or new human studies supported by the ICs, and Program 3 would coordinate programs and integrate data. Although Program 3 would serve as the support system for Programs 1 and 2, it also would involve some research. The MAPGen Working Group envisions MAPGen as a 10-year initiative, with Programs 1 and 3 ready to begin immediately and Program 2 being phased in.

Discussion Highlights

- Council members agreed that the proposed initiative would be transformative, particularly with respect to disease classification. Many problems with disease phenotype definition arise from definitions based on nineteenth-century pathology and from therapies geared toward end-stage phenotypes. There is a real need to reclassify or redefine disease.

- Molecular imaging and biomarkers should play important roles in understanding the relationships among phenotypes.

- Dr. Weinmann pointed out that, although ICs support much research examining underlying mechanisms, the research is disease-based according to the mission of each IC. MAPGen would be derived from traditional NIH mechanisms such as the R01, but the science would fall outside the mission of any individual IC. Council members also noted that generating the types of hypotheses addressed by standard R01 mechanisms would take a large amount of work.

- Psychobiological components of disease, such as stress and resilience, also should be considered, although these might be difficult to capture with MAPGen.

- Dr. Weinmann noted that, although the project could be done at many levels, it would have to be large to be truly transformative. Overlap among the three programs would be needed to facilitate information sharing.

- Council members cautioned that phenotyping is crucial but highly challenging. They also urged DPCPSI to talk with the Gene-Environment Interaction Group.

D. Library of Integrated Network-based Cellular Signatures (LINCS)

Dr. Alan Michelson defined the Library of Integrated Network-based Cellular Signatures (LINCS) initiative as one that would generate a set of perturbation-induced molecular activity and cellular feature signatures. These signatures can be used to infer mechanism-based relationships among perturbing conditions, as well as associations among responding cellular components. Feasibility for such a project was demonstrated by a paper, published in *Science* in 2006, which described a connectivity map that used gene-expression signatures to connect small molecules, genes, and disease and to classify drugs functionally. LINCS would extend connectivity mapping in all dimensions by expanding the number and type of perturbation conditions (such as small molecules,

silencing RNA, and environmental factors), cell types (such as immortalized cells, primary cells, and cells representing different diseases), and phenotypic assays.

The transformative potential of LINCS lies in its application to a wide range of basic, clinical, and translational biomedical problems, for example the reconstruction of predictive biological networks and the elucidation of how human genetic variants cause disease. Along with MAPGen, LINCS also could aid in the classification of diseases based on molecular criteria. It also could aid in target-based design of new drugs and combination chemotherapies, in the development of novel molecular diagnostics, and in the next generation of disease-association studies.

Dr. Michelson described program implementation as a three-way block of perturbations, cell types, and phenotypic assays, which would generate data to be analyzed, integrated, and applied. Functional annotations with existing knowledge also would be used to inform data generation and analysis. Dr. Michelson proposed two phases. The first would award a data coordinating center and establish a LINCS database to support exploratory studies and optimize selection of cells, perturbations, and assays; develop new and cost-effective wet lab and computational technologies; and standardize nomenclature and experimental protocols. The second phase would select experimental systems from Phase 1 for more in-depth study, with a goal to generate richer datasets. This phase would apply new technologies developed in phase 1, provide support to new computational investigators, validate novel hypotheses generated by LINCS, apply LINCS to various biomedical problems, and facilitate transition of these systems to IC support for wider application.

Discussion Highlights

- Generating data from a limited number of cell types and reconstructing the complexities of human tissue will present initial challenges, and special care must be taken in the selection of starting material. Council members suggested talking with cancer network researchers, as cancer represents a series of perturbations and researchers in this field have had some success with human tissue. Council members also suggested consideration of the spatial aspects of networks (that is, how signaling in a particular pathway might differ at different places in the cell).

- LINCS will integrate well with the Clinical IMPACT Awards program and the MAPGen initiative.

- Dr. Michelson noted that all the elements are in place to begin Phase 1 immediately. The LINCS Working Group envisioned implementing Phase 1 by requiring a pre-application, then selecting the most complementary ideas and inviting applications from those investigators.

- Dr. Michelson clarified that LINCS would not be restricted to cellular signaling. Instead, it would represent all biological processes. Dr. Michelson also noted that LINCS would advance existing efforts by attempting to coordinate, standardize, and

integrate data, which at present is difficult. LINCS would aim to create synergy among existing databases.

- Some Council members also suggested focusing on a next-generation model, where LINCS could generate data for a new set of genetically defined primary cell types, rather than coordinate data from existing cell types.

E. Discussion and Vote

Dr. Skirboll reminded the Council that its vote would represent a recommendation to DPCPSI and the NIH Director that a concept is worth pursuing. CoC discussed the best process for voting (early versus late, ranking versus yes-no) and how best to report to their individual IC advisory councils. Some members noted that it was not clear whether a formal vote would provide anything in addition to the discussion that had already taken place. Overall, a motion was made and seconded for a sense of the Council that all three concepts meet Roadmap criteria and are scientifically sound. The Council expressed strong enthusiasm for the Clinical IMPACT Award program and MAPGen and posed questions for DPCPSI to consider for LINCS. The motion passed (15 for, 2 against).

A motion was made and seconded for the Clinical IMPACT Award program to be approved for further development. CoC agreed that this is a Roadmap-worthy effort that could promote a paradigm shift in the mechanism of supporting science. The motion passed unanimously (17 for, 0 against).

A motion was made and seconded for MAPGen to be approved for further development. The motion passed unanimously (17 for, 0 against).

A motion was made and seconded for LINCS to be approved for further development. Although several Council members expressed concern that the concept is not sufficiently refined at this point, other members felt that the central idea has been developed nicely and could benefit from further refinement. The motion for further development passed (9 for, 8 against).

XII. CLOSING REMARKS

Dr. Skirboll summarized and noted that the Council's discussion was of great help to DPCPSI and to NIH overall. She reported that RCDC will roll out soon, and DPCPSI will notify CoC when it does. Council members also will be given copies of a trans-NIH collaboration report and a DHHS collaboration report.

Although the Council members have experience with NIH as a result of serving on their individual IC councils, they might not be fully informed about NIH-wide activities. Future meetings should include efforts to widen Council members' knowledge. Dr. Skirboll noted that the field of portfolio analysis, and DPCPSI's efforts in that area, is one area that should be discussed further. DPCPSI welcomes suggestions from Council members on other areas they would like to hear more about. Council members suggested briefings on OAR, ORWH, OBSSR, and ODP; learning about initiatives that have not

worked; a pre-meeting acronym dictionary; and an explanation of how Roadmap initiatives are coordinated versus trans-NIH activities outside Roadmap.

Council members also suggested a 1-day meeting. A third of the day would be devoted to informing Council about structure and planning, a third would be devoted to science, and a third would be devoted to issues CoC can help with. Dr. Skirboll noted, however, the difficulty in balancing discussion time, items that must be on the meeting agenda, and items CoC would like to see on the agenda. Members also agreed that a single, 2-day meeting each year, supplemented by web-based communications and teleconferences, might be desirable.

XIII. ADJOURNMENT

Dr. Skirboll adjourned the meeting at 11:34 a.m. on November 21, 2008.

XIV. CERTIFICATION

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

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Lana Skirboll, Ph.D.
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Acting Director, Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director
National Institutes of Health