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

Council of Councils Meeting
June 19, 2015

Meeting Minutes

I. WELCOME

James M. Anderson, M.D., Ph.D., Chair of the NIH Council of Councils, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. The meeting began at 8:15 a.m. on Friday, June 19, 2015, in Building 31, Conference Room 10, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson noted that Drs. Emery N. Brown, Judy E. Garber, Lila M. Gierasch, Nancy L. Haigwood, James E. Schwob, and Gilbert C. White, and Mr. Hakon Heimer were unable to attend the day's meeting. Dr. Craig J. McClain participated via teleconference. Dr. Anderson extended an official welcome to the eight Council members who were cleared by the ethics office and are now official and voting members: Drs. Sharon Anderson, Mary Lindsey Carnes, Terry L. Jernigan, Vivian S. Lee, Kimberly K. Leslie, Guillermina Lozano, and Keith A. Reimann, and Mr. Hakon Heimer. The other meeting attendees are identified below.

Dr. Anderson noted the upcoming retirement of Dr. Jack Whitescarver, Director, Office of AIDS Research, effective July 1, 2015, and recognized his many contributions to AIDS research. He also announced that Dr. Robert W. Eisinger will serve as Acting Director, OAR, pending recruitment of a new Director.

Following introductions and announcements from Franziska B. Grieder, D.V.M., Ph.D., Executive Secretary for the NIH Council of Councils, Dr. Anderson reviewed the day's agenda. He referred Council members to the DPCPSI Director's Report, included in their meeting books, which highlights upcoming meetings, funding opportunity announcements (FOAs), and other NIH news of interest.

A. Attendance

1. Council Members

Council Members Present

Chair: James M. Anderson, M.D., Ph.D., Director, DPCPSI, OD, NIH
Executive Secretary: Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI, OD, NIH
Philip O. Alderson, M.D., Saint Louis University, St. Louis, MO
Sharon Anderson, M.D., Oregon Health & Science University, Portland, OR
Marlene Belfort, Ph.D., University of Albany, Albany, NY
Carlos D. Bustamante, Ph.D., Stanford University School of Medicine, Stanford, CA
Mary Lindsey Carnes, M.D., M.S., University of Wisconsin-Madison, Madison, WI

Janice E. Clements, Ph.D., The Johns Hopkins University School of Medicine, Baltimore, MD
Ana M. Cuervo, M.D., Ph.D., Albert Einstein College of Medicine, Bronx, NY
Steven T. DeKosky, M.D., University of Virginia, Charlottesville, VA
Susan F. Goekler, Ph.D., M.C.H.E.S., Directors of Health Promotion and Education, Washington, DC
Barbara J. Guthrie, R.N., Ph.D., F.A.A.N., Northeastern University, Boston, MA
King K. Holmes, M.D., Ph.D., University of Washington, Seattle, WA
Terry L. Jernigan, Ph.D., University of California, San Diego, La Jolla, CA
Norma Sue Kenyon, Ph.D., Wallace H. Coulter Center for Translational Research, University of Miami School of Medicine, Miami, FL
Vivian S. Lee, M.D., Ph.D., M.B.A., University of Utah, Salt Lake City, UT
Kimberly K. Leslie, M.D., University of Iowa Hospitals and Clinics, Iowa City, IA
Guillermina Lozano, Ph.D., The University of Texas MD Anderson Cancer Center, Houston, TX
Terry Magnuson, Ph.D., University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC
Craig J. McClain, M.D., University of Louisville School of Medicine, Louisville, KY
Norbert J. Pelc, Sc.D., Stanford University, Stanford, CA
Keith A. Reimann, D.V.M., University of Massachusetts Medical School, Boston, MA

Council Members Absent

Emery N. Brown, M.D., Ph.D., Massachusetts Institute of Technology, Harvard Medical School, Massachusetts General Hospital, Cambridge, MA
Judy E. Garber, M.D., M.P.H., Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
Lila M. Gierasch, Ph.D., University of Massachusetts, Amherst, MA
Nancy L. Haigwood, Ph.D., Oregon Health & Science University, Beaverton, OR
Hakon Heimer, M.S., Schizophrenia Research Forum/Brain and Behavior Research Foundation/Cure Alliance for Mental Illness, Providence, RI
James E. Schwob, M.D., Ph.D., Tufts University School of Medicine, Boston, MA
Gilbert C. White, II, M.D., Blood Research Institute, Blood Center of Wisconsin, Milwaukee, WI

2. Liaisons

Juliana Blome, Ph.D., M.P.H., Associate Director for Science Policy, Planning & Analysis, Office of Research on Women's Health (ORWH), DPCPSI
David M. Murray, Ph.D., Director, Office of Disease Prevention (ODP), DPCPSI
William Riley, Ph.D., Acting Director of the Office of Behavioral and Social Sciences Research, DPCPSI
Elizabeth L. Wilder, Ph.D., Director, Office of Strategic Coordination (OSC), DPCPSI

3. Presenters

Paul M. Coates, Ph.D., Director, Office of Dietary Supplements (ODS), ODP, DPCPSI
Emmanouil Dermitzakis, Ph.D., Professor, Department of Genetic Medicine and Development, University of Geneva Medical School
Susan E. Koester, Ph.D., Deputy Director, Division of Neuroscience and Basic Behavioral Science, National Institute of Mental Health (NIMH), NIH

Jon R. Lorsch, Ph.D., Director, National Institute of General Medical Sciences (NIGMS), NIH
Stephanie Murphy, V.M.D., Ph.D., Director, Division of Comparative Medicine (DCM), ORIP, DPCPSI
George M. Santangelo, Ph.D., Director, Office of Portfolio Analysis, DPCPSI
Elizabeth L. Wilder, Ph.D., Director, OSC, DPCPSI

4. NIH Staff and Guests

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

B. Meeting Procedures

Dr. Grieder reviewed the following:

- Council members are Special Government Employees during Council meetings and therefore are subject to the rules of conduct governing Federal employees.
- Each Council member submitted a financial disclosure form and conflict of interest statement as a Federal requirement for membership on advisory councils. Financial disclosures are used to assess real and perceived conflicts of interest, and Council members must recuse themselves from the meeting during discussion of items for which conflicts have been identified.
- Time has been allotted for discussion between the Council members and presenters, but time for comments from other meeting attendees is limited. The public may submit comments in writing; instructions are available in the *Federal Register* notice for the meeting, which was published on May 5, 2015.
- Minutes from the January 30, 2015 meeting have been published on the DPCPSI website. The minutes from this meeting also will be published there.

C. Future Meeting Dates

The next Council meeting will be held on September 1, 2015. Council meetings in 2016 will be held on January 29, May 20, and September 9.

II. UPDATE ON COMMON FUND PROGRAMS

Dr. Elizabeth Wilder, Director, OSC, DPCPSI, provided an update on the Common Fund Program, including new and continuing programs for FY 2016–2017. During the past year, the Council heard about three new concepts, specifically the Molecular Mediators of Physical Activity (PA), Enabling Exploration of the Eukaryotic Epitranscriptome (E4), and Gabriella Miller Kids First Pediatric Research (Kids First) programs. She also updated the Council on several continuing programs, namely the Illuminating the Druggable Genome (IDG) program and the Knockout Mouse Phenotyping (KOMP2) initiative.

Dr. Wilder explained that the proposal review process involved presentation of the new program concepts. The Council cleared the PA concept in 2012, E4 in 2014, and Kids First in January 2015. The Kids First program was initiated in response to Congressional authorization and funding of the project. The Directors of the NIH Institutes and Centers (ICs) provided input on the proposals in spring 2015 and received updates throughout the different stages of concept development. In April and May, the NIH and DPCPSI Directors reviewed the final proposals for the five programs. The PA, Kids First, and KOMP2

programs have received approval for FY 2016, and the IDG program will continue as a pilot for one more year, and the E4 program will be reconsidered next year. Dr. Wilder expressed satisfaction with the strong programs that will be supported in FY 2016.

The PA program's goals of developing a catalog of molecular transducers of physical activity in humans and performing preliminary functional characterization of key emergent transducers will be achieved through four initiatives. The first initiative involves a clinical study of well-phenotyped fit or sedentary adults exposed to defined physical activity regimens. A second initiative will focus on the multi 'omic analysis of tissues derived from participants and from parallel animal studies to identify the molecular mediators in physical activity. The third initiative will provide consortium coordination and data integration support to allow data mining by the broader community. The fourth initiative will support animal studies to produce data that are parallel to the human data and to explore function and mechanisms at the molecular level. The expected budget is $170 million (M) over 5 years. A trans-NIH PA Working Group is being led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute on Aging (NIA).

The Kids First program will develop a data commons resource for the pediatric research community incorporating data on both structural birth defects and pediatric cancer. The program includes three initiatives focused on the sequencing effort of patients from existing cohorts, including cohort identification and enrichment; the development of a pediatric data commons to compile collected data and provide robust linkage to existing data resources; and data mining, target discovery, and development projects. The expected budget is $63M over 5 years. The Kids First Working Group is a trans-NIH group that has worked diligently to initiate the program in a short timeframe.

The KOMP2 program aims to systematically phenotype knockout mice to define the *in vivo* function of mammalian genes and identify new models of human disease. It is a collaborative effort which is co-led by the Common Fund Program, the National Human Genome Research Institute (NHGRI), and ORIP that ensued from an earlier trans-NIH effort to generate mutant ES cells for all of the genes in the mouse genome. Initiatives include the production and characterization of knockout mice, phenotyping of knockout mice, and a database and data coordination center for the phenotyped data. The KOMP2 Working Group is led by co-chairs from the National Institute on Deafness and Other Communication Disorders (NIDCD), ORIP, and NHGRI, and the Common Fund will provide matching dollars for the phenotyping efforts by the ICs. The expected budget is $94.25M over 5 years.

Discussion Highlights

- The KOMP2 program is producing standardized mice with an emphasis on phenotyping data. The program will need to consider the balance between production from ES cell mutations or clustered regularly interspaced short palindromic repeats (CRISPR) technologies, as well as ways to encourage deposits into repositories and dataset maintenance and sustainability.

- The PA concept, which was cleared by the Council in 2012, is focused on a shorter term exercise and a systematic 'omics approach to the human body's physiologic responses to exercise.

- The Kids First program will build its data collection in phases, ultimately making available both sequencing data from existing cohorts and the data associated with the cohorts themselves. Details about data collection will be provided as the Data Coordination Center launches.

- The goal of the Data Commons for the Kids First program is to start with data that are gathered through the program, but allow fluid integration across other types of datasets, similar to the

vision for the Big Data to Knowledge (BD2K) program, which is on the Council's agenda for its September 2015 meeting.

- DPCPSI has developed a new process for vetting concepts to better engage the Council in a meaningful way, starting with a strategic planning workshop in July 2015 to develop initial concepts. These concepts will be vetted through an online forum, then discussed and refined by the IC Directors. The strongest proposals will be shared with the Council at its January 2016 meeting. A second phase of strategic planning will follow, with fleshed-out concepts presented again to the Council for additional comments.

III. SUMMARY AND UPDATE OF THE MARCH 28 ABRF/NIH CORE MEETING

Dr. Anderson provided an update on NIH efforts to enhance the efficiency of research core facilities. Support for cores is a substantial part of the NIH portfolio, including Center-type grants and Cooperative Agreements. The total support for P30, P50, P60, and U54 awards, for example, was $2B in FY 2013 out of a $29B budget. Analysis found that approximately one-half ($1B) was spent directly on core facilities and one-quarter each on administrative and research support. Redundancy of support exists within institutions as well as within and between NIH funding ICs, but the level is challenging to document. Dr. Anderson disavowed the myth that NIH policies discourage sharing, noting that many institutions are motivated to manage cores efficiently, but management practices vary.

In 2009, under the American Recovery and Reinvestment Act of 2009 (ARRA), NIH supported a supplement program to provide funds to consolidate cores and increase efficiency in core management. The support was for the purpose of consolidating multiple cores into single, presumably more efficient cores. Stipulations included that the consolidated core facilities be widely available as institutional resources while operating within the scope of the original award, and awardees were required to share best practices. Twelve ICs participated in this funding, which could be used to hire personnel who implemented the core consolidation, purchase equipment, or conduct minor alterations or renovations to bring the cores together. A total of 80 applications were received, and 26 administrative supplements were awarded, ranging from $300,000 to $1.3M, for an aggregate total of $22M provided.

Recipients submitted a final progress report responding to 13 questions about their program's outcome. The ICs successfully combined between two and five cores each, with some combining a core across ICs and others combining with university-supported cores. The NCI supported the highest number of cores among the ICs and successfully combined two cores four times, at four different institutions. In all cases, awardees reported an increase in net users, services provided, or both. Twenty of the awards created combined cores that increased users up to threefold. Centralized processes included billing, purchasing, scheduling services, and tracking. One observation was that costs were lower for such items as supplies and licenses because the institution could bargain as a larger group.

Annual program income generated by individual cores in 2009 was $2.3M, and after consolidation in 2013 it was $4.3M. Program income can be used under the umbrella of the existing parent grant to support the expansion of ongoing activities. Efficiencies from the successful consolidation of cores resulted from institutional centralized oversight and planning, advanced methodologies and technologies not available in the smaller cores, cross-training of staff, enhanced consultation and analysis of complex data, and unified standard operating procedures. Dr. Anderson referred members to a commentary on these achievements published in *The Journal of Biomolecular Technology* (2015;Apr 26(1):1–3).

The NIH and Association of Biomolecular Research Facilities (ABRF) co-sponsored a workshop in March 2015 to identify lessons learned and best practices for enhancing the efficiency of cores. The

workshop included NIH presentations on its policies and funding of cores and discussions by ABRF members about their experience and perspective on obstacles and solutions to enhancing efficiency, as well as the management of cores from a central perspective. NIH participants—which included DPCPSI in the Office of the Director, the Office of Extramural Research, National Center for Advancing Translational Sciences (NCATS), National Cancer Institute (NCI), and DPCPSI—were joined by the National Science Foundation (NSF). More than 100 people attended presentations and panel discussions, including seven research deans and several centralized core administrators. Dr. Anderson recognized the assistance provided by Council member Dr. Terry Magnuson, who attended as a discussant. A summary of the meeting is available on the DPCPSI and ABRF websites (http://dpcpsi.nih.gov/sites/default/files/NIH-ABRF%20Workshop%20Report_Complete_06-22-15.pdf).

Recommendations from the workshop for both the institutions and NIH will be considered. Research institutions were encouraged to better understand their core facility portfolios and to improve management to increase efficiencies, capacity, and competiveness. Specific recommendations included developing institutional core strategy plans to facilitate coordination among all institutional facilities, supporting continuing education of core scientists, and investing in specialized expertise in financial management and better use of tools. Challenges faced by core directors—such as the need for communication tools, grant writing support, equipment management, and mechanisms for researcher training and education—should be addressed. In addition, strong governance of research core facilities, including building trust and transparency, should be established. Administrative, reporting, and other burdens could be reduced by determining the services that qualify for fixed amounts, developing and disseminating best practices, and developing inventories to understand cores on their own campus.

Participants also recommended that the NIH improve communication and coordination of issues related to NIH-supported core facilities, enhance cross-agency coordination about core facility sharing and co-investments, and convey through FOAs to applicants/grantees that sharing is encouraged through facilities and services. Opportunities should be identified to facilitate coordination between and among Clinical and Translational Science Award (CTSA) opportunities, Cancer Center support grants, and other funded core facilities. In addition, guidance about internal versus external rates for use of core facilities should be developed, and a system of unique core identifiers should be developed for use in grant applications and reports to facilitate reporting and citations indexing. The NIH policy regarding reporting publications resulting from core facilities also should be clarified.

Discussion Highlights

- Universities have benefited from core consolidation by reduced duplication and lower costs, but leadership at those institutions has had to provide strong commitment and rationale to implement the changes needed for greater efficiency. ABRF continues to consider ways to engage a greater number of research deans.

- Opportunities may exist to coordinate core grants of the CTSA and Cancer Center programs. Cores could be made accessible to private-sector companies, provided that indirect costs are addressed appropriately.

- Members encouraged the NIH to actively encourage consolidation and cross-utilization of cores for fiscal efficiency, particularly with investigators who prefer autonomy. Application requests could indicate that use of existing cores or a commercial service provider is allowable. Another option is to require a list of the existing cores at one's institution and indicate how the proposed core will be different.

IV. OFFICE OF DIETARY SUPPLEMENTS—RESEARCH OVERVIEW AND STRATEGIC PLANNING

Dr. Paul M. Coates, Director, ODS, ODP, DPCPSI, presented ODS' research overview and strategic planning activity. The Dietary Supplement Health and Education Act of 1994 (DSHEA), which amended the Food, Drug, and Cosmetic Act, defined dietary supplements in the marketplace. DSHEA established a framework regarding the U.S. Food and Drug Administration's (FDA) purview in regulating dietary supplements. The Act also established rules for what a label should contain and gave the FDA the authority to write dietary supplement-specific Good Manufacturing Practices (GMPs). In addition, DSHEA created the Office of Dietary Supplements at the NIH. DSHEA defined a dietary supplement as a product intended to supplement the diet and containing one or more of the following: vitamin, mineral, amino acid, other dietary substance, or herb or another botanical, excluding tobacco. A dietary supplement cannot be represented as a conventional food and cannot be manufactured with the intent to cure, treat, diagnose, prevent, or mitigate disease.

Dietary supplements are regulated as foods, rather than as drugs. The products do not need to be registered with the FDA, receive prior approval, or be proven effective or save although companies are expected to maintain backup material for any claims. There are no mandatory formulation standards, but some assurance is required for new (post 1994) ingredients. To ban a supplement, the FDA must prove "a significant or unreasonable risk of illness or injury." The FDA's post-marketing activities are limited to monitoring product information and safety. The Federal Trade Commission (FTC) regulates advertising; although manufacturers cannot make disease prevention or treatment claims, they can make other claims about health promotion or reduction the risk of chronic disease. These claims could be that a product or ingredient will improve the structure or function in the body. Examples of dietary supplements include: micronutrients (vitamins and minerals); macronutrients (fatty acids, protein, amino acids); herbs (St. John's wort, ginkgo biloba); phytochemicals (lycopene, isoflavones); zoochemicals (creatine, bee pollen); and other items, such as probiotics, glucosamine, and melatonin.

Dr. Coates reported that sales of dietary supplements in the United States have risen dramatically from 4,000 products totaling $8.6B in sales in 1994 to as many as 85,000 products totaling approximately $35B in sales in 2013. Approximately one-half of the adult population in the United States uses dietary supplements on a regular basis. Use varies by individual: most take one or two dietary supplements, but others take dozens; most people supplement moderately and primarily with nutrients, whereas others take megadoses or are adventurous with their intake. Categories of the most likely users include women, older people, wealthier people, and those with healthy lifestyles. "Nutritional insurance" and "optimal health" remain top reasons for use, as well as special purposes (e.g., treatment of health problems and performance enhancement).

The ODS undertakes its mission to strengthen the knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, and disseminating research results. The Office also works to educate the public to foster an enhanced quality of life and health for the U.S. population. It conducts systematic reviews of the efficacy and safety of dietary supplements in collaboration with the Agency for Healthcare Research and Quality Evidence-Bases Practice Center Network, with the particular objective of assisting the NIH in the development of research agendas and to inform public policy. Other partners have included the National Center for Complementary and Integrative Health (NCCIH, formerly the National Center for Complementary and Alternative Medicine) and FDA on such topics as ephedra and probiotics, NHLBI and others on omega-3 fatty acids, and numerous partners on vitamin D and calcium.

For example, the ODS conducted a systematic review of a series of evidence reports on omega-3 fatty acids. The reports featured results from controlled clinical trials through observational studies. Health

endpoints spanned cardiovascular disease, asthma, cancer, cognitive function, mental health, and others, with exposures encompassing dietary supplements and fish. Approximately one-quarter of the studies were of good quality, but another quarter were of poor quality. The overall evidence from the aggregate studies was inconclusive beyond one highlight in secondary prevention of cardiovascular disease for those who already had evidence of heart disease. Only one-third of the reports described adverse events, suggesting incomplete and inadequate reporting.

Concerns about dietary supplement products have involved issues of identification particularly with regard to plants, characterization of the product, contamination, and reproducibility for long-term studies. Following Congressional concerns about the need for validated analytical methods and reference materials for common botanicals and other dietary supplements, the ODS created the Analytical Methods and Reference Materials (AMRM) program in 2002. The AMRM was designed as a partnership among Federal agencies and the private sector to develop, validate, and share analytical methods, as well as to produce and share reference materials. Applications include the characterization of test substances by academic researchers, the implementation of GMPs and product formulation by industry, and review of label claims and safety by regulators.

Dr. Coates also described ODS activities pertaining to vitamin D. The human body contains many receptors for vitamin D. Evidence for the enthusiastic use of vitamin D—particularly to help with cancer, diabetes, cardiovascular disease, and immune function—comes primarily from observational studies, with little evidence from controlled intervention studies and no evidence about dose response. In response to declarations of widespread deficiencies and the need for public health certainty about vitamin D, the ODS supported and led the systematic exploration of issues surrounding it. Activities included convening an Institute of Medicine panel to review the Dietary Reference Intakes for Vitamin D and Calcium in collaboration with others in the Canadian and U.S. Federal Governments and updating a systematic review to inform the activities of a 2014 workshop on issues about vitamin D for primary care physicians.

ODS has also led development of the collaborative Vitamin D Standardization Program (VDSP), with the goal of standardizing 25-hydroxyvitamin D [25(OH)D] measurement in humans in national health surveys to the U.S. National Institute of Standards and Technology (NIST) Standard Reference Materials and their Reference Measurement Procedure. Additional objectives included developing a research program on 25(OH)D and the laboratory standardization of its measurement; encouraging assay manufacturers and clinical and research laboratories toward standardization; and promoting the use of standardized data in patient care and public health activities. In addition to the development of a Reference Measurement System and successful collaboration with assay manufacturers, the VDSP collaborated with the Centers for Disease Control and Prevention (CDC) to develop its certification program for large clinical laboratories and manufacturers, and with NIST and the Vitamin D External Quality Assessment Scheme to develop the world's largest laboratory testing system for 25(OH)D. The Program also has developed models to standardize vitamin D values in previously conducted studies, as well as in six national health surveys around the world.

Dr. Coates highlighted several ODS collaborative activities. With the National Center for Complementary and Integrative Health, the ODS supports the NIH Botanical Centers Program, a program that has been in place since 1999. The ODS allocates 50 percent of its research budget to fund and co-fund investigator-initiated research across the NIH, as well as partnerships with other agencies and contracts. To help researchers and consumers, the ODS and National Library of Medicine launched a dietary supplement label database in 2013, with the aim of including labels of all dietary supplements sold in the United States (www.dsld.nlm.nih.gov/dsld/). This publicly available database includes photos of labels and searchable fields. It included 43,000 labels as of May 2015, with 1,000 labels added each month. The ODS and U.S. Department of Agriculture (USDA) developed a dietary supplement ingredient database that includes analytically verified supplement labels for the purposes of estimating nutrient exposure

(www.dietarysupplementdatabase.usda.nih.gov). Two exercises conducted to date address adult and children's multivitamins and minerals, and another exercise is planned on green tea extracts. The ODS' website is consumer-oriented, providing material in both English and Spanish, including access to a variety of fact sheets on commonly consumed dietary supplement ingredients.

Finally, Dr. Coates described the ODS' strategic planning process. The ODS has been guided by successive strategic plans since 1999. The emphasis has remained on three areas: research, resources for investigators, and resources for consumers. These are reflected in the nearly completed 5-year plan for 2015–2020. The process includes a progress report for agency and public input that was completed in January 2015; a draft plan for input to be completed by July 2015; and release of the final plan in the fall of 2015. The progress of implementing the strategic plan will be continuously monitored.

Discussion Highlights

- Regulation of supplements and botanical compounds varies around the world. The Australian government, for example, regulates the whole class of compounds as therapeutic goods and manufacturing companies must meet a preregistration requirement. Efforts to harmonize rules are ongoing across the European Union.

- ODS has no role in the regulation of cannabis and, to date, no role in conducting research in this area.

- Council members expressed appreciation for the robust section on vitamin D for health professionals available on the ODS website.

- Most dietary supplement products in the United States are made according to reasonable quality standards, as many manufacturers of the most commonly consumed products also are pharmaceutical companies. The FDA is responsible for monitoring dietary supplement products in the marketplace but does not have premarket authority. The NIH remains concerned about product characterization issues, and the NCCIH has implemented a policy that requires all of its principal investigators to adhere to a set of principles called Product Integrity Evaluation.

- Caffeine is present in dietary supplements at widely varying levels, and the ODS is working to identify issues that are associated with energy drink use, as well as formulations in the marketplace.

- Individuals will process supplements differently based partly on their genetic makeup. Questions about bioactive components and their metabolism, both by the microbiome and by the products of an individual's genome, represent a new frontier for research.

V. PERSPECTIVE FROM NIGMS

Dr. Jon Lorsch, Director, NIGMS, presented the NIGMS' perspective on biomedical research and the Institute's position within the NIH. The NIGMS promotes basic research on living systems to lay the foundation for advances in disease diagnosis, treatment, and prevention. The Institute also enables the development of the best trained, most innovative and productive biomedical research workforce possible. It includes five programmatic divisions, specifically the divisions of Cell Biology and Biophysics, led by Dr. Cathy Lewis; Pharmacology, Physiology, and Biological Chemistry, which is recruiting for a division director; Biomedical Technology, Bioinformatics, and Computational Biology, led by Dr. Susan Gregurick; Training, Workforce Development, and Diversity, which will be led by the newly hired

Dr. Alison Gammie; and Genetics and Developmental Biology, led previously by Dr. Judith Greenberg, NIGMS Deputy Director, with recruitment underway.

An overarching goal of the NIGMS strategic plan is to refocus the Institute's priorities toward investigator-initiated research. Historically, NIGMS has been oriented toward investigator-initiated research and had a 99 percent investigator-initiated portfolio. Between 1998 and 2003, when the NIH budget doubled and ensuing years, the amount of the NIGMS budget committed to targeted research increased dramatically, with investigator-initiated research comprising only 80 percent of the portfolio.

To sustain the fundamental biomedical research enterprise optimally and remain focused on its mission, the NIGMS has begun to re-balance its portfolio. From FY 2002 to FY 2013, the number of applications increased notably, whereas the number of funded applications remained relatively unchanged, with the success rate falling from 40 to 20 percent in that time period. Efforts to re-balance toward investigator-initiated research have shown initial success, with the application success rate rising to 25 percent in FY 2014. The portfolio reorganizations and adjustments to procedures and priorities are having a positive impact, but the NIGMS intends to sustain an increase in the success rate for individual investigators.

Dr. Lorsch described numerous challenges faced by the NIGMS, which span the efficiency of how the NIGMS uses its funds, the academic business model, issues concerning trainees and the scientific workforce, peer review, and reproducibility, among others. These challenges converge on a central challenge of how biomedical research is funded. The model used predominantly by the NIGMS to fund biomedical research is a project-based funding model. This model creates a number of inefficiencies in the system, including that investigators are constrained by needing to focus on specific aims and are asked to predict what they will be doing 4 or 5 years in the future; furthermore, investigators break up their research into smaller research projects for which they seek distinct grants, which is inefficient.

An analysis of the distribution of NIGMS grantees in relation to their total NIH direct costs showed that 5 percent of the grantees receive one-quarter of the NIGMS funds for grants, and 20 percent receive one-half of the money. This problem was highlighted in a *New York Times* article that described the maldistribution of reimbursements from Medicare and Medicaid for physicians. Shifting distribution may maximize the return on investment for the NIGMS and NIH. For example, an analysis of PI productivity showed that awarding another R01 to someone who already has $400K in grant funding results in one additional paper, whereas giving an R01 to a new PI or someone who will otherwise have nothing results in five papers. The NIGMS supports grantees with an aggregate $400M annually in direct costs; recouping 10 percent of that amount would return $40M into the system.

An increasing number of studies dispute the contention that project-based distribution based on merit, and hence support of the best scientists, is the best approach. Metrics of productivity and scientific impact have been shown to not scale proportionally with funding over a certain direct-costs threshold; raw productivity decreased for those with grants above $700,000 or $750,000 in direct costs. In terms of a return on the taxpayers' investment in biomedical research, supporting a new investigator with a lower application percentile score but greater productivity than an established investigator may be the most efficient way to use the funds. Other NIH ICs—such as the National Heart, Lung, and Blood Institute—have conducted extensive analyses of their portfolio and agreed that productivity and impact of the science do not scale proportionally with funding over a certain funding level. Similarly, a recent paper that examined British life sciences laboratory size reported diminishing returns as a function of size.

To optimize the output and the quality of science, the NIGMS is conducting an experiment to fund research programs instead of using the project-based funding model. This approach will increase the stability of funding to enhance investigators' willingness to focus on ambitious scientific projects and to approach that science in a creative manner. It also will increase the flexibility for investigators, allowing

them to follow new directions as ideas arise in their work. Such flexibility was what allowed basic scientist Dr. Andrew Fire at the Carnegie Institution of Washington to move from a failed control experiment on the development of worms, *Caenorhabditis elegans*, to the discovery of RNAi; 25 clinical trials are now ongoing using siRNAs. Funding research programs instead of projects also will improve the distribution of funding, thereby increasing overall scientific productivity and the chances for important breakthroughs. Researchers will spend less time preparing grant applications and have more time conducting research, and the time spent on reviewing applications will be reduced.

The Maximizing Investigators' Research Award (MIRA) will provide one NIGMS research grant per PI using the new R35 mechanism. MIRA will be larger ($750,000) and longer (5 years) than a current NIGMS R01 and not be tied to specific aims. Reviews will be based on the track record of the investigator, including consideration of the service and contributions to workforce development, and their overall research ideas. The budget could be modulated based on competing reviews to avoid abrupt termination of research groups, and separate panels and modified review considerations will be implemented for early-stage investigators. Dr. Lorsch noted that the NCI also uses the R35 mechanism for its Outstanding Investigator Award (OIA).

The MIRA implementation plan is starting with a pilot of a moderate number of applications to test the MIRA application and review process. The first group of applications encompasses established PIs who have NIGMS funding already and either have two or more NIGMS R01s or only one NIGMS R01 that funds more than $400,000 in direct costs. Approximately one-quarter of the eligible pool has applied for the MIRA in the first round. The NIGMS recently released a second FOA for new investigators and early-stage investigators at the assistant professor level, and applications will reviewed by separate review panels and criteria. Dr. Lorsch stated that if the pilot phase is successful, the NIGMS will expand the program to include all PIs working on questions relevant to NIGMS' mission.

Discussion Highlights

- A multipartite scheme for metrics is being developed to evaluate the MIRA project. Citation-based metrics may be used to understand what is happening in the system. In addition to overall performance, evaluation should improve support for NIGMS-supported scientists and the breadth and diversity of the NIGMS portfolio should increase.

- The increased age at which a PI receives his or her first R01 is a multicomponent concern, and the results of FOAs for junior investigators will be reviewed carefully to determine the effects.

- The flexibility of the budget in an investigator-based funding model was lauded. Funding criteria will be considered at multiple levels, including the study section, the Institute program, and the NIGMS Council.

- The NIGMS Office of Program Evaluation and Assessment has considered the percentage and characteristics of the investigators who participated in the first round of MIRA and noted a significant number of junior investigators, many of whom had recently received their second R01.

- The NCI's OIA varies from MIRA with a larger budget, a 7-year length with a mid-grant programmatic review, and 50 percent research effort. MIRA includes a 51 percent research effort, which precludes an investigator receiving both an OIA and MIRA together.

- An investigator who holds a MIRA cannot have other NIGMS research funding, but is not precluded from receiving funding from other NIH ICs.

- Members lauded MIRA as a means to return to idea- and discovery-based science.

VI. REVIEW OF GRANT APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[1] Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Council would represent a real or perceived conflict of interest. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect. The *en bloc* vote for concurrence with the initial review recommendations was affirmed by all Council members present. During the closed session, the Council concurred with the review of 107 ORIP applications with requested first-year direct costs of $39,735,554 and with the initial review of 909 Common Fund applications (Pioneer, New Innovator, and Transformative Research Award applications) with requested first-year direct costs of $979, 609, 272.

VII. GENOTYPE-EXPRESSION—SCIENTIFIC PRESENTATION AND DISCUSSION

A. The Genotype-Tissue Expression (GTEx) Project

Dr. Susan E. Koester, Deputy Director, Division of Neuroscience and Basic Behavioral Science, NIMH, NIH, provided a perspective on the GTEx Project. Many NIH ICs face a similar challenge of translating the findings from genome-wide association studies (GWAS) that link genomic variants to a disease or trait. These variants frequently are found in noncoding regions of the genome and reveal few hints about how the variants ultimately change cellular activity. The aim of the GTEx Project is to understand how to decode the genomic variation to find causal genes and pathways for genetically complex diseases.

The first step in this translation is to discover how or whether genomic variants alter gene expression. The hypothesis is that disease-associated variants in noncoding regions may affect disease through gene regulation. A genomic variant that correlates with altered gene expression is referred to as an expression quantitative trait locus (eQTL). The challenge has been to discover eQTLs in disease-relevant tissues, because many of these are difficult to access in living humans. In addition, large sample sizes are needed to reach statistical power to measure eQTLs in disease-relevant tissues and cell types directly.

The GTEx Project's goal is to discover eQTLs using a wide array of tissues from postmortem donors. More than 30 different tissue types have been gathered from donors in rapid autopsy or organ tissue donation settings. Each donor underwent whole-genome and whole-exome sequencing to discover genomic variants, and each tissue sample collected underwent RNA sequencing to measure gene expression.

The Common Fund program agreed to support a pilot phase to evaluate the feasibility of the GTEx Project. Milestones included sample collection from the necessary number of donors in a reasonable timeframe, and the Project succeeded in collecting more than the minimum 10 donors per month for the 18 months of the pilot collection phase. Another benchmark of success was ensuring that tissues were of sufficient quality to provide useful information, which was accomplished by 70 percent of the samples

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[1] For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure applied only to applications that were discussed individually, not to '*en bloc*' actions.

from 12 or more organs or tissues having an RNA Integrity Number (RIN) with a score of 6 or better. Based on these feasibility results, the NIH and Common Fund leadership agreed to support the project in full.

The GTEx scale-up goal includes tissue collection from 900 postmortem donors and complete RNA sequencing on approximately 20,000 samples from these donors, as well as associated clinical, demographic, and histopathological information. Investigators also are developing novel methods for statistical analysis of this specialized set of data. A tissue and data access system has been established for the project, and a survey was conducted on the ethical, legal, and social issues surrounding consent for postmortem tissue donation. Epigenomic and other assays on a subset of the collected tissues also are underway.

Dr. Koester described the process from collection through sequencing. A fibroblast cell line is developed from a skin sample and frozen. Whole-exome and whole-genome sequencing are performed on blood samples, and a lymphoblastoid cell line is developed. Whole brains are collected when appropriate (e.g., in situations where the donor has not been on a ventilator for more than 24 hours) and sent to an NIH-supported brain bank. Peripheral tissues are collected from multiple organ sites and fixed rapidly in PAXGene tissue, with a subset of tissues stored as flash-frozen aliquots; all of the tissues undergo a histopathologic review. DNA and RNA are extracted from these samples. The DNA is stored, and the RNA quality is measured and then sequenced to 70 million reads.

Donor selection criteria include adults ages 21 to 70 years, with all racial/ethnic groups and both sexes accepted. A postmortem interval of 24 hours or less is required, and in practice has averaged 6 to 8 hours. Medical exclusionary criteria are similar to those used for organ and tissue transplant settings. The GTEx Analysis Working Group recently published a series of manuscripts describing the analysis of the pilot collection of 175 donors.

Dr. Koester expressed appreciation to the trans-NIH working group members, the Consortium members, whose efforts show team science at its best, as well as to the donor families, without whose generosity this research would not be possible.

Discussion Highlights

- Dr. Koester clarified that brains are not collected from donors who are brain dead and maintained on a ventilator.

- The primary tissue collection is nearly completed. Whole blood is not currently stored, but rather, lymphoblastoid cell lines were derived, which was a standard practice at the time of project initiation. Primary fibroblast lines have been frozen and could be used to generate induced pluripotent stem cells.

B. The GTEx Pilot Analysis: Multi-Tissue Gene Regulation in Humans

Dr. Emmanouil Dermitzakis, Professor, Department of Genetic Medicine and Development, University of Geneva Medical School, presented a GTEx pilot analysis on multi-tissue gene regulation in humans. GWAS aim to understand how genes contribute to phenotypes, such as diseases that may develop later in life. Space and time are required for the manifestation of genetic effects, but a genetic signal can be influenced by many other factors, such as environmental effects or specific human behaviors. Because different regions of the genome are active in various tissues, understanding how a signal manifests itself in cells and results in a particular phenotype is crucial. The study of tissue complexity in the context of

the genetic information will elucidate the biology of the disease, beyond the risk variance provided by GWAS studies.

GWAS have identified hundreds of common DNA variants associated with multiple complex diseases and traits. However, more than two-thirds of GWAS single nucleotide polymorphisms (SNPs) lie in noncoding regions, and associated genes are not located in close proximity. eQTLs provide an approach for molecular phenotyping, specifically looking at the *cis* and *trans* environments for increased levels of gene expression. Many studies have shown trait-associated SNPs enriched for eQTLs, but challenges remain in using eQTLs to interpret disease associations. These include measuring eQTLs in disease-relevant tissues or cell types, obtaining most human tissue types, and needing large sample sizes for statistical power. These challenges are being addressed through the full-scale GTEx Project that is being funded through the NIH Common Fund. Tissues from the 900 GTEx Project donors will provide the power to detect both *cis*-eQTLs and *trans*-eQTLs, the latter of which tend to have a smaller effect size and are more difficult to correct for multiple testing. In addition, The Broad Institute will be performing whole genome sequencing on all 900 individuals, which will facilitate work toward identifying the causal variant. The Illumina 5M exome technology currently being used will be replaced by whole exome sequencing.

The pilot GTEx phase included an average of 28 tissues per donor, with the eQTL analysis focused on nine of the tissues. The next stage will examine gene expression clustering, using eQTLs in 45 tissues. Gene expression can be viewed in terms of total gene expression or from the exon perspective, which provides a score for splicing.

The pilot project was restricted to *cis*-eQTLs and looked at 1 megabase, or 100 kb in some cases, away from the transcription start site; used PEER correction (probabilistic estimation of expression residuals) to remove undesirable effects; and employed a method called matrix eQTL to perform eQTL analysis and permutations, thereby randomizing the expression data with specific covariates to control for the multiple testing (in terms of multiple SNPs per gene and the number of genes tested). Results showed 2,000 to 2,200 eQTLs per tissue, as well as a linear relationship between the sample and the number of eQTLs discovered. Approximately 10 to 20 eQTLs were identified from each sample, depending on the tissue, with a core number located around the transcription start site where the regulatory elements were the densest.

Dr. Dermitzakis described a replication study to verify the eQTL findings using an independent sample from a study published in 2011. High replication between the two sets was found, as well as notable functional enrichment. Further analysis across the multiple tissues revealed two classes of eQTLs: tissue-specific and tissue-wide, with a large gap between them. The amount of eQTL discovery per tissue also increased as more tissues were added, suggesting that tissue specificity can be helpful in interpreting GWAS.

Allele-specific expression can be examined in sequencing data and used to differentiate and confirm the activity of eQTLs. For variants within the transcript in an individual that is heterozygous, the reads can be partitioned when they overlap with that particular variable position by those with the T or the C. If the eQTL in an individual is homozygous or if the tissue does not have the eQTL, both alleles will show in the same way and the ratio is not distorted. If that eQTL is heterozygous, however, more T than C is seen.

Allele expression also can be studied tissue-wide by looking for different degrees of allele-specific expression. Allelic imbalance is biased expression that allows comparisons between individuals and within individuals across tissues. Because allele-specific expression represents a genetic effect, the ratio of alleles in a comparison of muscle to brain from one individual is more similar than it would be between two brains of two different individuals.

Dr. Dermitzakis' group studied alternative splicing by examining the origins of specific characteristics of splicing QTLs. Alternative splicing also can be measured by specific aspects of internal structure of the transcript. His team found that the eQTL seeker can discover more complex events, total transcript effects, and a functional enrichment of those eQTLs for splicing in annotation from ENCODE. Network module QTLs, or the correlated behavior of genes that changes from one individual to another depending on genotypes, are useful to discover variants that have an impact on multiple genes and a network structure with a larger impact on biology than individual eQTLs. Another aspect is to look at variants sometimes discovered as eQTLs that are in regions that have an effect on the transcript itself, rather than in regulatory regions. This means that an eQTL that correlates with exactly the genotype of introducing a stop codon could be a stability effect of the transcript rather than a regulatory effect. Effects can be classified after the relevant issue is understood, allowing exome and genome sequencing studies to include the diversity of transcripts among the different tissues and how these tissues are relevant to the specific phenotype under study.

Researchers have been able to link eQTLs to GWAS variants. Dr. Dermitzakis shared several examples, including effects seen in a hypertension study by the Wellcome Trust Case Control Consortium in 2007 that indicated association even though the gene studied was not highly expressed. Thus, to classify a gene's importance based on the level of expression of a relevant tissue may be misleading. This work allows the integration of multiple tissues into what could be a systems understanding of a disease. In the pilot GTEx Project, the particular phenotypes of eQTLs linked to GWAS with respect to the nine tissues were enriched. For example, blood can be used to interpret many of the signals that are associated with inflammatory bowel disease. Researchers could begin building profiles about the relative contribution of each tissue to the genetic susceptibility of a disease, such as inflammatory bowel disease, and that information could be integrated across all diseases. Organs could be studied to determine which are more likely to contribute to the susceptibility of multiple disorders. GTEx can be used as a reference set to explore personalized interpretation, not only of individual variants but also of whole tissue or whole body effects, without ever assaying expression on these other individuals.

Dr. Dermitzakis summarized the pilot findings to date, which include an unprecedented catalog of eQTLs in multiple tissues, eQTL tissue specificity estimates, and the first glimpse in the effect of genetic variation in diverse tissues and organs of the human body. In addition, the pilot project has shown the importance of GWAS and other disease variant interpretation and causal effects.

Discussion Highlights

- The GTEx Project will parse out racial diversity during Phase 1, but ethnic diversity would require a larger sample size than is available. Gender, which is expected to be an approximately equal male/female ratio, also will be considered. Regarding the levels of expression of paternal versus maternal genes, imprinting using GTEx data has been considered; in multiple individuals, imprinting has been observed to be reversed in IGF2.

- GTEx can work with induced pluripotent stem cells, and one approach would be to reach differentiation of the induced pluripotent stem cells into tissues, generate the same type of population cells, and compare them to what the Project already has found. The generation of tissues from induced pluripotent stem cells would isolate much of the environmental effect, likely strengthening the genetic signal and allowing a higher power eQTL analysis to discover even smaller effects.

- Sequencing remains expensive per cell. Synergies exist between single-cell analysis and GTEx activities, but some tissues with greater single-cell effect are easier to capture than others because of the cell collection, preservation, and separation processes.

- The GTEx Project would be interested in developing a collection of pediatric donors, but ethical issues would need to be addressed before any collection occurred.

- Biological variability of the samples was seen in tissues that were found unstable with RNA that degraded quickly, particularly kidney tissue. Only small effects were seen in surgical samples. A larger sample size can alleviate some of the effects of quality and variance related to collection and processing.

- The Project has experienced remarkable success in its recruitment of tissue from 900 donors. It was unclear at inception if the pilot would achieve its tissue and sequencing goals.

- The GTEx Project has not provided new insights into how QTLs work, but the combined efforts of GTEx and a number of genomic projects, including Enhancing GTEx, ENCODE, and HapMap, are converging toward consideration of population variation in functional assays that integrate existing annotation and known genetic variation.

VIII. SUMMARY OF ORIP'S DIVISION OF COMPARATIVE MEDICINE WORKSHOP HELD ON APRIL 7–8, 2015: ONE HEALTH

Dr. Stephanie Murphy, Director, DCM, ORIP, DPCPSI, reported on an April 2015 ORIP Division of Comparative Medicine workshop on One Health: Integrating the Veterinarian Scientist into the Biomedical Research Enterprise. One Health is the integrative effort of multiple disciplines working together to attain optimal health for people, animals, and the environment. One of the biggest challenges facing One Health scientists and clinicians has been in communicating how the One Health concept can advance the NIH mission. The workshop aimed to provide information and advice on how the One Health concept could advance the NIH mission regarding research programs and training. The planning committee consisted of veterinarian scientists, clinicians, and research investigators from both basic and applied research, all of whom have been engaged in different facets of the One Health community and many were long-term ORIP and NIH grantees.

The workshop included 34 speakers and more than 170 registered participants, including staff from 20 NIH ICs; representatives from Federal agencies, including CDC, FDA, and USDA; NIH-supported extramural and intramural researchers; and representatives from the private sector. Dr. Carolyn Henry, University of Missouri, provided a keynote presentation on One Health challenges for the 21st century, which highlighted the need to refine the definition of One Health, change the culture of science and medicine as it relates to One Health, communicate the One Health message effectively, and better predict and prepare for the future with regard to One Health issues. Session topics included case studies from multidisciplinary teams that used animal and human subjects to study infectious diseases, cancer, and neurological diseases; panel discussions of One Health perspectives from various centers, Federal agencies, and biopharmaceutical organizations; and panel discussions on NIH-supported training programs that use the One Health concept, including ways to improve training of multidisciplinary teams and integration of veterinarian scientists within these investigative teams.

Participants provided recommendations related to training, the workforce pipeline, strategic planning, high-impact health challenges, and interagency collaborations. Training could be enhanced by either expanding the number of available slots in the Medical Scientist Training Program (MSTP) or supporting

a separate Veterinary MSTP program. In addition, comparative training in alternative models and training outcomes data are needed. Other suggestions included having unique T and F training programs specifically for veterinary students and veterinarians, expansion of the loan repayment program to include public practice veterinarians in One Health areas and more promotion of collaborations across Federal agencies in areas of need.

Participants also noted that national student mentoring networks are needed to address and highlight the role of veterinarians in research. These mentoring networks would not just be limited to veterinary students and veterinarians but would include other health professional and biomedical research trainees. Outreach promoting examples of longitudinal veterinarian scientist training "tracks" and their accessibility was also encouraged. Participants also recommended that the Physician-Scientist Workforce Working Group Report and its recommendations be leveraged as part of the ongoing strategic planning process within NIH . To address high-impact health challenges, national clinical studies platforms utilizing naturally occurring animal diseases should be supported, development and support for naturally occurring animal disease approaches should be provided, the research agenda should be broadened to include the impact of human-animal interactions on human health, and existing consortia should be leveraged as appropriate. Current interagency collaborations should be leveraged, including the joint NIH and USDA/National Institute of Food and Agriculture Dual Purpose with Dual Benefit: Research in Biomedicine and Agriculture Using Agriculturally Important Domestic Animal Species program and the joint NIH and NSF Ecology and Evolution of Infectious Diseases Program.

After the April workshop, a May–June 2015 newsletter from the Fogarty International Center highlighted the One Health workshop and described how the NIH encourages veterinarians to consider research careers. Members of the CTSA One Health Alliance (COHA)—which is composed of 10 veterinary schools partnered with medical and other colleagues through CTSAs—who attended the conference are preparing proposals for a Collaborative Innovation Award in the CTSA program, applying One Health concepts discussed at the workshop. In addition, the Association of American Veterinary Medical Colleges is developing communication channels and resource-sharing opportunities between Federal agencies regarding One Health and is collecting data and metrics on long-term outcomes of biomedical research training programs for veterinarians.

ORIP has posted the meeting summary and a video recording of the workshop on its website at dpcpsi.nih.gov/orip/cm/reports. Potential FOAs that could be developed include (1) the development of reagents and biological tools to characterize naturally occurring disease conditions in cats and dogs that can inform or be used for the assessment of parallel disease states in humans and (2) competing or administrative supplements for ORIP-supported resources to engage veterinarian scientists. ORIP's plans include potentially developing a summary paper on the role and impact of veterinarian scientists in multidisciplinary teams to enhance visibility of veterinarian scientists and the One Health concept as applied to the NIH mission. Relative to training, DCM is considering expanding its training and research program grant portfolios to include participation on the parent F32 and R03 mechanisms. These actions would allow ORIP to extend support of veterinarian scientist postdoctoral trainees at the individual as well as institutional levels and would provide transition support between a K01 grant and the first R01 grant in veterinarian scientist career pathways for early-career veterinarian-scientists. ORIP also could identify and summarize available mentoring resources for developing veterinarian scientists on its website.

Discussion Highlights

- The One Health umbrella is large and encompasses climate change as an aspect of environmental health.

- ORIP and the NCATS have been engaged in discussions regarding the possibility of a large-animal consortium to keep up with scientific needs and direction.

- One of the case studies presented at the One Health workshop highlighted research on infectious diseases pursued jointly by human and animal health scientists. Researchers studying viruses in animal populations in Africa worked in parallel with a clinician-scientist to try to predict some of the human pathogens that might emerge and to identify current pathogens and commonalities. The NIH and NSF participate in an interagency collaborative effort focused on the ecology of infection and diseases.

- Communication and forums that facilitate discourse are appreciated by the One Health community. , COHA and the American Veterinary Medical Association are keenly interested and actively promoting the One Health perspective.

- The concept of One Health will require large amounts of data and analytics. The workshop included discussions about access to clinical databases for companion animals as a pre-clinical step in screening some of the therapeutics for other diseases. Reagents and tools to link data were among the needs identified by workshop participants.

IX. UPDATE ON DPCPSI PORTFOLIO ANALYSIS ACTIVITIES

Dr. George M. Santangelo, Director, OPA, DPCPSI, provided an update on DPCPSI portfolio analysis activities. OPA's mission is to improve data-driven decision-making at the NIH. This is accomplished by coordinating portfolio analysis activities at the NIH; conducting thorough analyses for NIH senior leadership; tool development; database management and data cleaning; planning and hosting seminars, workshops, and symposia; and provision of opportunities for crosstalk within the NIH community, including the Portfolio Analysis Interest Group and blog (*The Analyst*). OPA also assists staff across the NIH with analyses, which on occasion includes collaborations to develop tools or generate case studies. Training occurs in formal classes and *ad hoc* training sessions, as well as through such materials as user manuals, FAQs, and instructional videos available on the OPA website. OPA also is tasked with developing a science of portfolio analysis through new tools and approaches and is building a community of experts that involves the government, academia, and private sector. Its network has grown significantly during the past four years through consultation business, training sessions, and service to the NIH ICs. The Office has developed a training portal with courses that range from introductory portfolio analysis to advanced offerings in IN-SPIRE analysis; network analysis and bibliometrics courses are forthcoming. OPA uses existing data-driven approaches to characterize research investments and their outcomes, and develops and delivers effective approaches and methodologies. Dr. Santangelo described the OPA tools in development: *iCite* (bibliometrics), *iTrans* (tracking translational research), *iTech* (patent analysis), and a disambiguation tool called *iClean*.

OPA is also developing content analysis methodologies to better facilitate document clustering and other machine-learning approaches that can allow exploratory visualization of the NIH portfolio. Staff can compare portfolios, both within the NIH and across the biomedical research spectrum globally. Dr. Santangelo illustrated his explanation in part by displaying the results of an IN-SPIRE analysis that examined and clustered the portfolios of two ICs, including the titles, abstracts, and specific aims of all R01 grant applications in FY 2012.

iCite is a web-based use of the Relative Citation Ratio (RCR) metric to overcome limitations of commonly used bibliometrics in measuring the influence of a publication or group of publications on other scientists. Metrics with serious limitations include publication counts, impact factor, citation rates,

and the h-index. In contrast to these cruder methods, RCR is an article-level metric that normalizes the citation rate of each paper based upon its co-citation network. It is calculated as the article citation rate divided by the expected citation rate based on the field that the paper is in. RCR is an article-level metric that uses the number of cites per year, and it may change over time with the accrual of new citations in both the numerator and the denominator.

Scalable to large portfolios containing tens of thousands of articles, as well as applicable to the individual article level, RCR's novel approach focuses on the co-citation network, that is, the papers that are alongside the article of interest in the reference list of citing papers. Each time a paper is cited, approximately eighteen additional papers are added to the co-citation network. A benchmark provided by a linear regression analysis is used to ascertain how the RCR of a paper or group of papers relates to the larger corpus. A paper that is never cited has an RCR of zero, an RCR of 1.0 is average, and a paper with an RCR greater than 20 is exceptionally highly cited and impressive in terms of influence on the field. The co-citation network is a good match for the area of science. For example, given of an NIH-funded paper that described new conotoxin-like peptides of possible clinical utility, the co-citation network was found to grow over time as new subfields of science showed interest and appeared in the network.

Each article has an RCR denominator that represents is specific field. Other denominators, such as the Thomson Reuters Ratio, use a "multidisciplinary" category for all paper in *Science*, *Nature*, *PloS ONE*, and other broad-scope journals. In contrast to multidisciplinary categories that generate the same denominator for very different areas of science, RCR is article-level and can identify the area of science for each paper within those journals. For example, an analysis of two papers on hepatitis C and their co-citation networks, which overlap but are not identical, showed that the RCR for the paper in *PloS ONE* was 4.2 compared to the RCR for the paper in *Nature*, which was 3.0, suggesting that the *PloS ONE* paper has greater influence in the context of its scientific field.

A validation study using subject-matter experts in the NIH intramural program found 300 of 700 papers with more than two responses per paper and considered the possible correlation between relative citation ratio values and expert' perception of the papers that were in the study. These were matched to the expertise of the investigators and spanned the NIH portfolio. A 1-5 scale was used, and a strong correlation with overall evaluations was found. Reviewers decided on a paper's overall value based primarily on likely impact, followed by robustness, importance, human health, and method. In addition, RCR performed much better than the Thomson Reuters Ratio in identifying potentially problematic outliers due to a low expected citation rate.

An analysis of publications of NIH investigators with continuous R01 funding from FY 2003 to FY 2010 showed sharp divisions between papers when using the impact factor of the corresponding journals. Using a metric that measures the influence of each article independently, by normalizing according to its area of science and over time, many papers overlapped with the top ten percent of papers in the journals in the top quintile. In addition, analyses of journals in which NIH investigators published frequently showed dramatic difference between RCR values and impact factors. For example, *The Journal of the Acoustical Society of America*, with an impact factor of 1.6, had a higher RCR median than *Nucleic Acids Research*, which had an impact factor of 7.1. There was also significant overlap between the RCRs of papers in many low impact factor journals and those in three journals with high impact factors (*Nature*, *Science*, and *Cell*).

NIH PIs with continuous R01 funding through two consecutive four-year periods were found to have stable influence as ranked by both RCR and weighted RCR. A study at NIGMS showed that R01 projects submitted for competitive renewal have higher weighted RCRs, relative to R01 projects for which there was no attempted renewal. The ICs are able to inform their portfolio review with this tool and other

bibliometric data in aggregate by discerning patterns and information that would otherwise be difficult or impossible to obtain.

Dr. Santangelo concluded his presentation with a brief description of *iTrans* and *iTech*. The former is a tool for mapping translational science that resulted from Dr. Griffin Weber's "Triangle of Biomedicine," which uses citation patterns to visualize the trajectory of research from discoveries in basic science to clinical trials and translation to patient treatment. The three points of the triangle represent human, animal, and cellular/molecular research. Based on Medical Subject Heading (MeSH) terms in papers that cite each other, OPA used *iTrans* to track the translational development of cancer immunotherapeutic agents, starting with basic research in 1987–1996 that focused on animal and cellular/molecular topics, through a translational stage of research in the 2000s, and culminating in human research, clinical trials, and successful treatment of patients in 2010–2014.

iTrans can plot in the aggregate—including entire journals, such as *Nature*, *Neuroscience,* and *The New England Journal of Medicine*—and can map publications to their correct positions on the triangle. In Dr. Santangelo's analysis of all NIH publications funded by active research grants in 2010, papers with human MeSH terms were found to mostly come from Institutional Review Board (IRB)-approved projects. For animal research, papers with animal MeSH terms were concentrated within the Institutional Animal Care and Use Committee (IACUC)-approved category of grants that funded those papers. Papers with cellular/molecular MeSH terms were mostly funded by projects that required neither IRB nor IACUC approval. IC-specific mapping of all publications funded by active research grants in 2012 showed the expected patterns.

iTech tracks patent, licensing, and start-up activities that resulted from NIH awards. Examples of *iTech* include linking an R01 award to an investigator who is a prolific patenter and who started a company, which continued to generate indirect patents that resulted from NIH investments, and a start-up that was linked to an NIH P50 award but was missed by NIH RePORTER.

Dr. Santangelo said that data-driven approaches, as exemplified by the use of these tools, can inform scientific portfolio management, but he stressed the importance of data cleaning. He reminded members that RCR is a validated, article-level replacement for widely used but inaccurate or imprecise measures of influence, and that tracking outcomes and measuring impact of investments require methods to monitor translation of basic research or patented discoveries into improvements in human health. The *iClean* and *iCite* are now being beta-tested by NIH staff; *iTrans* and *iTech* will follow.

Discussion Highlights

- Portfolio data are most often used in academia to promote faculty, and the tools being developed by OPA will be useful in this area.

- An analysis by the British Higher Education Council found that the average time from publication until impact was 15 years in the United Kingdom. The RCRs find that papers tend to reach their impact level relatively early and stay at that level, and the *iTrans* and *iTech* tools are the most useful for characterizing the scientific returns on investment and impact on decision-making.

- NIH staff and external stakeholders have expressed enthusiasm for the RCR as a method and potential replacement for the impact factor. The long-term goal is to continue validation studies, conduct beta-testing within the ICs, have it peer reviewed as a publication, and make it available to the broader community. The NIH was encouraged to share it with the Council of Deans for additional review.

- In addition to the availability of the public-facing tool, the computational code will be available on GitHub, ensuring transparency of both the method and the underlying data.

- Many types of bibliometrics are available and useful, provided the limitations of each are recognized. The M index, for example, is the H index factored for career duration and may be a fair metric for younger investigators or women who have taken time off for childbearing.

X. CLOSING REMARKS

Dr. Anderson thanked the Council members and speakers for their contributions at this meeting. He reminded the members that the next Council meeting will be held on September 1, 2015. The agenda will include a presentation by Dr. Francis Collins, NIH Director, as well as discussions of NIH's BD2K activity and the NIH-wide strategic plan.

XI. ADJOURNMENT

Dr. Anderson adjourned the meeting at 3:24 p.m. on June 19, 2015.

XII. CERTIFICATION

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

James M. Anderson -S

Digitally signed by James M. Anderson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=2000562943, cn=James M. Anderson -S
Date: 2015.07.17 15:38:37 -04'00'

July 17, 2015

James M. Anderson, M.D., Ph.D.
Chair, NIH Council of Councils
Director, DPCPSI, OD, NIH

Date

Franziska B. Grieder

July 17, 2015

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

Date