

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES**

**MINUTES OF THE ONE HUNDRED THIRTY-SIXTH MEETING OF THE
NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL**

May 22-23, 2012

The National Advisory Environmental Health Sciences Council convened its one hundred thirty-fifth regular meeting on May 22, 2012 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. Dr. Linda Birnbaum presided as Chair.

The meeting was open to the public on May 22, 2012 from 8:30 a.m. to 5:00 p.m. and on May 23, 2012 from 8:30 a.m. to 10:00 a.m. In accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), the meeting was closed to the public on May 23, 2012 from 10:00 a.m. to 12:30 p.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*.

Council Members Present

Kim Boekelheide, MD, PhD
Julia Brody, PhD
Marie-Francoise Chesselet, MD, PhD
Vivian Cheung, MD
Lisa Conti, DVM, MPH
Steven Dearwent, PhD (*ex-officio*)
Thomas Gasiewicz, PhD
Andrea Hricko, MPH
Howard Hu, MD, MPH, ScD
Randall Kramer, PhD
Mary M. Lee, MD
Grace LeMasters, PhD
R. Stephen Lloyd, PhD
Yvonne Maddox, PhD (*ex-officio*)
Jennifer Orme-Zavaleta, PhD (*ex-officio*)
Sem Phan, MD, PhD
Edward Postlethwait, PhD
Palmer Taylor, PhD
Viola Waghiyi
Deborah Winn, PhD (*ex-officio*)

NIEHS Staff

Joel Abramowitz, PhD
Karen Adelman, PhD
Kathy Ahlmark
Janice Allen, PhD
Beth Anderson
Bruce Androphy, JD
Robin Arnette, PhD
Joellen Austin
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard
Linda Birnbaum, PhD
Wanda Boggs
John Bucher, PhD
Katherine Burns, PhD
Christopher Campos, PhD
Danielle Carlin
Trisha Castranio
Honglei Chen, MD, PhD
Payal Chokshi, PhD
Alan Clark
Pamela Clark
Jennifer Collins
Gwen Collman, PhD
Helena Davis
Marilyn Diaz, PhD
Caroline Dilworth, PhD
Christina Drew, PhD
Dorothy Duke
Sally Eckert-Tilotta, PhD
Lisa Edwards
Maureen Evans
Symma Finn, PhD
Christine Flowers
Mary Gant
Antonio Gatling
Paul Gibson
Barbara Gittleman
Kimberly Gray, PhD
Astrid Haugen
Michelle Heacock, PhD
Jerry Heindel, PhD
Heather Henry, PhD

Jill Hesse, PhD
Michael Humble, PhD
Laurie Johnson
Melissa Jones
Paul Jung, MD, MPH
Ed Kang
Annette Kirshner, PhD
Thomas Kunkel, PhD
Cindy Lawler, PhD
Robin Mackar
J. Patrick Mastin, PhD
Elizabeth Maul, PhD
Kim McAllister, PhD
Steven McCaw
Rose Anne McGee
Liz McNair
Betty Mekdeci
Aubrey Miller, MD
David Miller, PhD
Fred Miller, MD, PhD
Nancy Mitchell
Ellen Moul
Sheila Newton, PhD
Aaron Nicholas
Liam O'Fallon
Ted Outwater
Andrew Passer
Richard Paules, PhD
Jerry Phelps
Kristi Pettibone
Edward Pope
Nicole Popovich
Molly Puente
Scott Redman
Leslie Reinlib, PhD
Jim Remington, RN
Elizabeth Ruben
Janine Santos, PhD
Thad Schug, PhD
John Schelp
Wynonah Sessoms
Daniel Shaughnessy, PhD
William Schrader, PhD
Carol Shreffler, PhD
William A. Suk, PhD, MPH
Kimberly Thigpen Tart, JD

Claudia Thompson, PhD
Frederick Tyson, PhD
Nigel Walker, PhD
Danielle Watt, PhD
Chris Weis, PhD
James Williams
Jessica Williams
Marva Wood
Leroy Worth, PhD
Richard Woychik, PhD
Darryl Zeldin, MD

Other NIH Staff

Della Hann, PhD, NIH
Sally Rockey, PhD, NIH

Members of the Public Present

Lynn Albert, MDB Inc.
Maureen Avakian, MDB Inc.
Ernie Hood, Scribe
Carol Kelly, MDB Inc.
Nancy Lamontagne, MDB Inc.
Pia MacDonald, SSS
Charles Novak, SSS
Leona Samson, MIT
Lesley Skalla, MDB Inc.
Bill Wade, SAIC
Robert Yates, SSS

I. Call To Order and Opening Remarks

Dr. Linda Birnbaum, Director of NIEHS and NTP, welcomed attendees and called the meeting to order. She mentioned that Council members Dr. Tom McKone and Ms. Elizabeth Yeampierre were absent from the meeting. She welcomed new Council members Dr. Vivian Cheung and Dr. Jennifer Orme-Zavaleta. She then asked all present in the room to introduce themselves, which they did.

II. Review of Confidentiality and Conflict of Interest

Dr. Collman reviewed the Conflict of Interest and Confidentiality procedures, which had been provided earlier to Council members in written form, and went over various other administrative matters.

III. Consideration of February 2012 Meeting Minutes

Approval of the February 2012 minutes was moved (Dr. Gasiewicz) and seconded (several), and Council voted unanimously to approve the minutes. She also noted the dates of the upcoming Council meetings for members to put on their calendars.

IV. Report of the Director, NIEHS

Dr. Birnbaum reported that the NIEHS Strategic Planning process is now in its final of the three phases. She reviewed the steps in the process since its inception. Since the last Council meeting in February, the last few steps of the development of the plan have been conducted, including writing the draft introductory section, incorporating ideas from the last Council discussion along with additional feedback obtained from meetings in March, such as SOT. The changes were captured in the near-final version posted on the NIEHS Strategic Planning website in early April for a last round of review. The feedback since has been overwhelmingly positive, she said. She shared the "cloud" diagram depicting the overlapping themes of the NIEHS mission, and related the most recent versions of the Mission Statement and Vision Statement. She also presented the eleven Strategic Goals that have emerged during the process, which were essentially the same as those presented in February. She noted that NIEHS sees that plan as a blueprint not only for NIEHS, but also in partnership with other environmental health organizations around the world. She said that NIEHS is now working on implementation strategies to define what will be done, when it will be done, and how much it will cost. She pointed out that as a five-year plan, everything will not be implemented right away. Rather, projects will be phased in gradually as others are gradually phased out. NIEHS divisions are currently reviewing the goals and developing implementation strategies to advance them. Leadership will ultimately consider those strategies, identify areas of overlap, and set institute priorities. The implementation strategies will also inform budget allocations by leadership over the next few fiscal years.

Reporting on legislative activities, she acknowledged the current situation of gridlock in Washington, with the prospect of no budget until after the presidential election or even during the subsequent lame duck session. She reported that the House Labor HHS allocation for FY2013, \$150 billion, is \$6 billion less than FY2012. Similarly, the Interior Environment allocation is \$1 billion less. Both reductions mean some painful cuts for HHS, she noted. The overall sense is that if the NIEHS budget can be held flat, it is doing well in the current situation.

In March, Dr. Collins testified on NIH funding for FY2013 before the House Labor HHS Appropriations Subcommittee, with much of the focus on the new National Center for Advancing Translational Sciences (NCATS). Dr. Collins spoke about the importance of the jobs created through NIH grants, which Dr. Birnbaum said is an important message.

Other issues raised included the new Alzheimer's disease initiative, the National Children's Study, obesity, tuberculosis, pancreatic cancer treatments, and priority setting at NIH.

Dr. Birnbaum reported that in light of recent Executive Orders and their interpretation by the Office of Management and Budget (OMB) and HHS, there will be increased oversight of federal funding and conferences. Part of that will be a 30% reduction in travel (not including Advisory Council travel) for FY2013 (based on FY2010 levels), including travel for conferences and training opportunities. For conferences, costs up to \$100,000 including travel must be approved by the NIEHS Executive Officer, and much more record-keeping and reporting will be required.

There is also a bill under consideration to increase research on pancreatic cancer, which would be an unfunded mandate if passed.

Dr. Birnbaum said that the frequency of her being invited to give congressional testimony has decreased, and that she has testified just once this year: on April 25, to a hearing by the House Committee on Science, Space and Technology Subcommittee on Investigations and Oversight, in a joint session with the House Committee on Small Business Subcommittee on Healthcare and Technology. The panels were interested in the *NTP Report on Carcinogens*, particularly regarding the Report's conclusion that styrene is reasonably anticipated to be a human carcinogen. That same day, Dr. Birnbaum met with the Chief of Staff of Congresswoman Lucille Roybal-Allard (D-CA), who is a member of the Labor HHS Appropriation Subcommittee and a strong supporter of environmental health research, with a special interest in NIEHS research related to breast cancer. Later that day, she also met with Rita Culp, who is on detail from the EPA Budget Office to the Senate Interior Environment majority staff, briefing her on NIEHS Superfund Research and Worker Training Program activities in 2012 and plans for 2013.

She shared recent scientific advances from NIEHS conducted or supported research. First, she summarized new findings from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, which suggest that fetal exposure to elevated levels of glucose and maternal inflammation due to obesity or hypertension affect fetal development. Data published by grantees at the Harvard School of Public Health suggest that long-term increases in temperature variability may increase the risk of mortality in different subgroups of susceptible older populations. A group at the University of Southern California has published new data estimating the yearly childhood asthma-related costs attributable to air pollution for Riverside and Long Beach, California.

In intramural scientific advances, researchers in the NIEHS Laboratory of Molecular Carcinogenesis have characterized the role of three key members of the Ccr4-Not complex within embryonic stem cell (ESC) self-renewal circuitry. That work may provide valuable insight into mammalian embryonic development, and facilitate the use of ESCs in various drug and cellular therapies. A study by Dr. Matt Longnecker and his colleagues in the Epidemiology Branch assessed the association of self-reported *in utero* exposure to tobacco smoke with the prevalence of obesity, hypertension, type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) in over 74,000 women 14-47 years of age. Increased odds ratios for each of the conditions were reported for women who had been exposed to tobacco smoke *in utero*. NTP investigators published a study that indicates that arsenic-transformed malignant epithelial cells recruit nearby normal stem cells into a cancer phenotype, thereby potentially increasing the number of cancer stem cells.

Turning to other institute news and highlights, Dr. Birnbaum recounted several important recent activities related to data sharing and integration, which are critical for solving environmental health problems. In February, NIEHS hosted a workshop on *Data Sharing Strategies for Environmental Health Science Research*, where several days of engaging discussion focused on issues such as the protection of privacy and confidentiality, Institutional Review Board issues, legal and regulatory issues, NIH programmatic and logistical considerations, and computational challenges. In May, Dr. Birnbaum participated on a federal panel at a similar meeting hosted by EPA. In March, NIEHS co-organized a workshop called *Engaging the Community for Research Success: What Scientists and IRBs Need to Know*, which was designed to increase the understanding of ethical, regulatory, and policy issues involved in conducting community-engaged research in national and international settings, including data sharing issues. In April, NIEHS hosted Todd Parks, who was recently named the US Chief Technology Officer. He spoke about the HHS Health Data Initiative.

As Dr. Birnbaum described, NIEHS continues to provide leadership on key public health initiatives and events. For example:

- The NIEHS-sponsored IOM Roundtable on Environmental Health Sciences, Research and Medicine recently held a 2-day meeting that explored the health implications and other pertinent aspects of “fracking.”
- The GuLF Study has reached a recruitment milestone, with more than 20,000 people now enrolled. The US Surgeon General has recorded a TV recruitment spot to be shown in the Gulf area to encourage participation.
- Nearly 20 postdoctoral fellows and institute staffers recently collaborated on curricula for Citizen Schools called “Healthy Lungs, Happy Life,” and also taught it through an afterschool enrichment program to local middle school students.

- Dr. Birnbaum also mentioned a new fellowship opportunity for mid-career scientists, a Tobacco Regulatory Science Fellowship sponsored by the FDA Center for Tobacco Products and administered by the IOM.

NIEHS was involved with several important meetings and events since the last Council meeting. In March, more than 150 scientists, experts, and stakeholders convened at the Centers for Children's Environmental Health and Disease Prevention Research annual meeting, held at NIH. In conjunction, the annual Partners for Environmental Public Health grantee meeting was held immediately following. In April, Dr. Birnbaum led the annual meeting in Boston of the NIEHS Environmental Health Sciences Core Centers. Following the meeting, she was part of a delegation that visited area neighborhoods to view environmental revitalization projects, and took part in a community forum with local government health and environmental officials, community advocates, and the public. In early May, Centers for Neurodegeneration Sciences grantees met at NIEHS for their annual meeting to discuss research being supported on Parkinson's, Alzheimer's, and other neurodegenerative diseases.

In March, nearly 250 trainers from the Worker Education and Training Program met in Fort Lauderdale for the National Trainers' Exchange, which gave trainers an opportunity to improve training methods and exchange ideas on effective health and safety training for emergency response workers. In April, the NIEHS-sponsored NAS Committee on Emerging Science for Environmental Health Decisions held a workshop on the endogenous and biological factors that influence individual variability in response to environmental exposures. In May, the Superfund Research Program held a unique meeting in Providence, Rhode Island, focusing on the social, psychological and economic impacts of living near contaminated waste sites. Also in May, NIEHS co-sponsored three international meetings. In conjunction with the WHO, leaders of the global initiatives on non-communicable diseases met in Paris with scientific experts on the role of the developmental origins of health and disease (DOHaD), to explore opportunities for incorporating exposure reduction into primary prevention. That event immediately preceded the 3-day Prenatal Programming and Toxicity (PPTOXIII) meeting, which NIEHS co-sponsored with SOT and several other organizations. Following the Paris events, NIEHS staff participated in a meeting at WHO in Geneva to solicit expert input on identifying a set of health indicators to be presented and discussed at the Rio+20 sustainability meeting in June.

Upcoming meetings include a Parkinson's Disease Premotor Symptoms Symposium to be held at NIEHS June 7-8, an Excess Folic Acid Workshop in Washington, DC, June 12-13, and a Systems Biology Workshop to be held June 14-15 by the NIEHS-sponsored NAS Committee.

Dr. Birnbaum reported that she was honored to have received several awards recently, including the 2012 Health Policy Hero Award from the National Research Center on Women & Families, the 2012 Science Leadership Hero Award from the Breast Cancer Fund, and an invitation to present the 12th Robert C. Barnard Environmental Lecture by the American Association for the Advancement of Science.

Other NIEHS and NTP staff members have also been honored recently. In group awards, Liam O'Fallon, Joseph "Chip" Hughes and Sharon Beard from the Division of Extramural Research and Training (DERT) received the HHS Green Champions "Good Neighbor" Award for their work on environmental justice for workers. The Office of Communications and Public Liaison received a Pegasus Award of Distinction for its video about the 2011 Summer Internship program at NIEHS.

Dr. Robert Sills, chief of the Cellular and Molecular Pathology Branch, was elected President of the Society of Toxicologic Pathology. Dr. Kenneth Korach received the Dale Medal, the highest accolade awarded by the Society for Endocrinology. Dr. Dale Sandler was elected into the Alpha Chapter of the Delta Omega honor society at Johns Hopkins Bloomberg School of Public Health. Dr. Walter Rogan was named an honorary fellow by the American Academy of Pediatrics. Dr. Karen Adelman was awarded tenure at NIH for her work in the Laboratory of Molecular Carcinogenesis. NIEHS grantee Dr. Kirk Smith of the University of California at Berkeley won a 2012 Tyler Prize for Environmental Achievement for his work on global indoor air pollution. Chris Long, who is NIEHS Deputy Associate for Management, was recognized by NIH for his leadership of the Combined Federal Campaign for charitable donations in North Carolina. Dr. Birnbaum congratulated staff and grantees for their achievements and recognition.

Dr. Gasiewicz asked whether there would be a pool of money or individual grants available for fracking studies. Dr. Birnbaum said that that was not yet known. She speculated that EPA might be getting some funding for environmental monitoring. She said several options were under discussion, and that NIEHS would certainly like to hear Council's view on how best to proceed.

Dr. Lee asked if the 30% travel and conferences cut would affect the money set aside for grants to provide support for conferences that various groups apply for. Dr. Birnbaum noted that the 30% cut is for travel, not conferences. Ms. Austin said the issue of funding for conferences is quite confusing, as new guidance is coming out every week from OMB or HHS. Right now, NIEHS is being asked to track and report, in a way not previously required, regarding conferences and meetings being supported with NIEHS funds, and on any grants whose principal purpose is to hold a meeting, such as R13s and U13s. She noted that the new guidelines are largely in reaction to a recent GSA conference that was deemed inappropriate, and she was pleased to report that there has been nothing improper in NIEHS practices.

Dr. Kramer said he was very impressed with the Strategic Plan and the process. He noted that Strategic Goal 6 mentioned health disparities and that Goal 10 focused on economic impact, and wondered whether that had implications for moving NIEHS more into the social sciences related to environmental health. Dr. Birnbaum said yes, but that it would take time to do so, and would represent new opportunities for partnerships with other organizations in the EHS community.

Dr. Brody noted that while the IRB conference was a good first step, there is still a long way to go in educating environmental health researchers about working with IRBs.

Dr. Hricko asked Dr. Birnbaum about the lawsuit brought by the Styrene Industry Research Center against HHS and NTP regarding styrene. Dr. Birnbaum replied that the case was currently on hold, and that she could not comment further on pending litigation.

Dr. Boekelheide asked whether NIEHS tracks the proportion of funds devoted to single-investigator-initiated grant activities versus interdisciplinary, integrated research grants. With the emphasis on the latter in the Strategic Plan, he asked whether a shift is anticipated in funding mechanisms. Dr. Birnbaum said no, since R01s could have more than one person involved, and we have the VICTER program to bring grantees together. Dr. Boekelheide also asked whether there would be a change over time in the proportion of funds from Requests for Applications (RFAs) given to certain ideas. Dr. Birnbaum said the institute had issued more FOAs, telling people what it is interested in. Dr. Collman noted that she normally gives a budget update in the February Council meeting, addressing some of these questions. She said that the funds set aside for solicitations ranged typically from 18-30%. She said the proportion set aside would be a subject for frequent Council consultation, particularly as the Strategic Plan moves forward.

V. Report of the Director, DERT

DERT Director Dr. Gwen Collman updated Council on DERT developments, beginning with staff activities. As always, DERT had a large presence at the SOT meeting in San Francisco in March, where program staff were available to interact with grantees. Noting several of the meetings that Dr. Birnbaum had discussed, she reiterated that staff members put an enormous amount of work into preparing and running such meetings and workshops designed to enhance collaborations. Dr. Collman mentioned that she had recently had an opportunity to meet with the Brown University Superfund Research Program investigators, and had met Senator Jack Reed (D-RI), who is well versed in environmental health matters. Dr. Leroy Worth and Dr. Linda Bass from the DERT review group recently went to a district meeting with Rep. Mel Watt (D-NC), and Dr. Caroline Dilworth participated in a webinar with people from Rep. Henry Cuellar's

(D-TX) district in southern Texas, highlighting several NIEHS programs for the local community.

Dr. Collman also updated Council on plans at CSR to revamp the review of EHS applications. CSR will reconstitute the Systemic Injury from Environmental Exposure (SIEE) Study Section as a Special Emphasis Panel (SEP). The SEP is expected to run from 2 to 3 review cycles, although that is not fixed, and the SEP could continue longer if needed. The SIEE grants will be percentiled against itself, although it is yet to be determined whether that will be according to the previous incarnation of the SIEE or just from the new version. After the trial run, CSR will evaluate whether the SEP should move on to permanent chartered status. That appears to be the goal at present, but through the trial run, the scientific community will be given enough time to generate a sufficient number of high-quality applications for review for a chartered study section. CSR and its Advisory Council will then have sufficient data to ensure the viability of the new study section. There would then be a formal vote at the CSR Advisory Council meeting. "The idea over the long term is to establish a chartered group with permanent membership to incorporate the needs of our field," said Dr. Collman. CSR anticipates a first meeting of the reconstituted SEP in February 2013, to review applications submitted in October and November, 2012. Dr. Collman reminded Council that it is best to request review by the SIEE in a cover letter along with applications.

Dr. Collman briefed Council on a new policy called Implementing Special Council Review of Application from Investigators with >\$1.5M Total Costs of Research Support. It was generated by a statement in the President's 2013 budget, and is part of NIH's approach to managing budgets in austere times. Dr. Collman announced that there would be a "dry run" of the council process for implementing the policy in the following day's closed session, piloting the process before it becomes official, to identify any potential kinks. Special Council Review (SCR) will be conducted for competing Research Project Grants (RPGs) – excluding P01s and other multi-component RPGs and multi-PI/PD applications, unless all Principal Investigators and Program Directors on the application exceed the threshold and applications. Applications submitted for RFAs are also excluded. Contributing to the \$1.5M threshold are existing grants or applications approved to be awarded at the time of the application in question. All single-PI funded grants are counted toward the threshold. For multiple PI/PD grants (P01s, multiple-PI R01s, etc.), only the portion of the funds attributed to the PI for the application under scrutiny are considered. To establish guidelines for SCR consideration, NIH has developed a tool for its internal database to compile a list of applications that exceed the threshold. There will be a presentation to Council by each of the Branch chiefs, with a written summary statement as well as a recommendation. The procedure for Council will be as with other Special Actions: a motion will be

requested, to either consider or not consider an individual application for funding, and a vote taken.

During the special review, Council is asked to consider as per these guidelines:

- Focus for new projects:
 - Unique opportunities to advance research
 - The project is highly promising
 - Distinct from other funded work of a well-funded investigator
- For renewal applications:
 - May also consider the value of continuing a productive project
 - Role this project plays in the investigator's research program and ongoing collaborations
- Consideration may also be given to the PI/PD's field of research
 - Different types of research (e.g., population sciences) may require greater funding than other fields
 - ICs, working with Council, may create defaults for some mechanisms and other RPG mechanisms and programs to simplify SCR

Dr. Collman mentioned that there was one application that fell into the SCR category lined up for discussion in the "dry run" to be held in the following day's closed session.

She introduced the finished product of the Partnerships for Environmental Public Health (PEPH) Evaluation Metrics Manual. She described it as "an outstanding product" that was two or more years in the making. Chapters include Partnerships, Leveraging, Products and Dissemination, Education and Training, and Capacity Building. She said that everywhere it has been rolled out so far, it has been greeted with tremendous enthusiasm. The manual is available on line at <http://www.niehs.nih.gov/pephmetrics>.

Dr. Postlethwait noted that in its original incarnation, the environmental health SEP only considered an application once, and that if it was not funded at that time it would go to a different panel for review of re-application. He asked whether that would still be the case with the new SEP, particularly if it only existed for two cycles. Dr. Collman replied that although she could not speak for CSR, she had received assurances that the intention is to keep the panel going and ultimately to gain approval for it to be a chartered study section, with no lapse intended. Dr. Birnbaum said that there is a very different mindset at work at CSR today, and that the organization is now more interested in working with the different communities to ensure that their reviews are conducted appropriately. She said the new director of CSR had assured her that they have no intention of doing away with the SEP, but most going through their processes to get it officially chartered as a study section. Dr. Postlethwait said that the issue of the panel percentiling against itself is also critical.

Dr. Gasiewicz said that the new SIEE SEP is very timely and very important. He asked whether the reviewers for the SEP would be the core set for the hoped-for study section, or strictly *ad hoc* reviewers. Dr. Collman replied that her impression is for the SEP reviewers to constitute a core group.

Dr. Hu asked about the SCR, noting that investigators would need a self-assessment to determine whether they were in the range of the threshold. Dr. Birnbaum replied, "This is not meant to be a bar to investigators having more than \$1.5 million in research funds." She said that for investigators who would get additional funding pushing them over that mark, Council is now required to take a look and ensure that the level of funding is appropriate. Dr. Collman noted that all of the 27 NIH ICs will be doing things slightly differently within Council procedures, and that some have more objective limits on the number of grants funded and the amount of money granted to investigators, and have already adopted procedures looking at those issues more carefully. Ultimately, she said, when money is tight, it's important to ensure that money going to more well-endowed research groups must be thoroughly considered. Thus, each institute has been given some flexibility to craft a process that meets the needs of its research community. Echoing Dr. Birnbaum's remarks, she said that "this is an attempt to have some consistent discussion and thought about decisions for funding across NIH, so that we're playing with a consistent set of rules across all of the institutes."

Dr. Lloyd asked Dr. Collman if the current portfolio had been analyzed to determine how many PIs the new rules would apply to if they were already in place. She replied that a full analysis had not yet been conducted, since the database tool to do so had only recently become available, but that such a study would be done in the future. Dr. Lloyd asked if the analysis would include funding from multiple ICs, and Dr. Collman replied that the software does account for monies from any sources. She added that the grants to be considered would be in the current round of Council consideration, and should be for ES research seeking NIEHS funding. She noted that it would be useful to determine how the procedure would apply to secondary funding.

VI. Concept Discussion: Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription (TaRGET)

Dr. Fred Tyson from the Cellular, Organs and Systems Pathobiology Branch presented the TaRGET concept to Council.

He said that NIEHS has been in a leadership position within the NIH community in supporting cutting edge research in the rapidly expanding field of epigenetics. The TaRGET proposal will take advantage of the momentum, infrastructure and technologies of several large-scale epigenomic programs such as the NIH Roadmap

Epigenomics Program, the ENCyclopedia Of functional DNA Elements (ENCODE), which is supported by NHGRI, and the International Human Epigenomic Consortium, along with several other international efforts.

He described the huge surge in epigenetics research in recent years, including a doubling of publications in the field every two years since the early 1990s. The field has also exploded thanks to new technologies such as high-throughput and next-generation sequencing. CHIP-seq has also added a tremendously useful capability of looking at protein interactions with chromatin and histone modifications. These advances have allowed rapid mapping of multiple cell types through epigenome-wide association studies (EWAS).

He said that NIEHS is particularly interested in epigenomics because the epigenome serves as the interface between the genome and the environment in common complex human diseases. The plasticity of the epigenome lends it to being modified or modulated within therapeutic or preventative strategies, offering a promising target for future interventions.

The great majority of NIEHS epigenetics research up to now has focused on DNA methylation as a readout of altered epigenetic processes perturbed by exposures. DNA methylation, he noted, is just part of the epigenomic process, and there is a need to better understand all of the epigenetic mechanisms, including histone modifications, non-coding RNAs, and more. He pointed out that "the more we learn, the more we know we don't know."

Leveraging the data and resources of the above-mentioned large-scale epigenomics projects, TaRGET will move beyond them to address how alterations to epigenomic marks and functional genomic elements might change with specific environmental toxicants.

TaRGET is proposed as a multi-phase strategy. TaRGET I, previously presented at Council in September 2010, will be out soon, and will support a group of R01s that examine various aspects of transcriptional regulation, encompassing epigenetic processes, chromatin dynamics, nucleosome positioning, regulatory genomic elements, transcription elongation, and non-coding RNA functional changes following environmental exposures.

TaRGET II is intended to be a resource to the community and address a few key issues that have been an impediment to the field moving forward. One key question involves the use of peripheral tissues such as blood to ask questions about phenotypes related to disease in inaccessible tissues such as the brain and other internal organs and tissues. Animal models would be used to compare changes in blood cells and other tissues following environmental exposures, in order to identify and validate these as

appropriate surrogates. TaRGET II would start with small proof-of-principle pilot studies looking at epigenomic changes in response to exposures to heavy metals, endocrine-disrupting chemicals and air particulates. They would look at specific modifications such as DNA methylation and histone modifications, as well as transcription binding factor sites, in mouse target cells and peripheral blood lymphocytes. The expected product is a database of exposures and catalog of changes in epigenomic marks and functional genomic elements in target and peripheral tissues, which would provide a critically important resource to the ES community of investigators pursuing research in epigenetics within exposure and disease pathogenesis contexts.

TaRGET III and TaRGET IV involve population-based studies. The goal is to challenge epidemiology studies to go beyond methylation, and to integrate epigenomic data with other datasets to inform human disease. This could be done by collecting additional datasets from existing cohorts, looking at other elements of chromatin dynamics, transcription factor binding sites and histone modifications. Integrative analysis would help inform health outcomes.

TaRGET III would supplement existing grants to develop more comprehensive analyses of exposed cohort peripheral blood leukocytes. Dr. Tyson shared a list of several studies that have biospecimens collected with environmental exposure data, which would be targets for acquiring enhanced datasets.

That would allow movement to TaRGET IV – integrative analysis. Conducting integrative analysis of epigenomic marks, regulatory DNA, GWAS and/or EWAS, will allow the emergence of new mechanistic paradigms of how environmental exposures impact a complex array of human disease outcomes. This strong focus on integrative analysis will mean that a substantial portion of the budget for these efforts would support bioinformatics capabilities, and a data coordinating effort would be needed for each grant supported.

The proposed timeline for the program involves TaRGET I being released by September 2012, with TaRGET II and TaRGET III pilot studies RFAs being released in December 2012. TaRGET IV RFA release would be October 2014, with awards by October 2015.

Dr. Chesselet was the first Council reviewer of the concept. She said she found the proposal to be extremely interesting and timely, and appreciated its comprehensive nature. She approved of the approach of initially using the R01 mechanism, leveraging the creativity of individual investigators. She said, "We absolutely have to do this," and was pleased that NIEHS is taking the lead in putting exposures into the equation. She felt that this line of research should be one of the institute's high priorities. She was concerned that TaRGET I may be too restrictive in its description of modifying elements,

and suggested that the RFA be more open to suggestion from investigators. She felt that TaRGET II was the most “interesting, compelling and urgent to do,” and that it should not be delayed too long, due to the importance of building consensus about the value of surrogate tissue.

For TaRGET II, she suggested adding evaluation of the use of post-mortem human brain, despite its difficulty. She suggested that NIEHS hold a workshop on that topic. She also said that IPS cells would be another tissue worth considering, perhaps also as a topic for a workshop. She recommended including information on therapeutics in the database associated with TaRGET II. She said she was positive on TaRGET III and TaRGET IV, and that taking advantage of the existing databases is very important. She said that TaRGET is “a very ambitious project, but it’s the right time to do it.”

Dr. Tyson said that the restrictive nature of TaRGET I noted by Dr. Chesselet would be expanded by using language indicating that the elements called for “include but are not restricted to...” He added that the Roadmap program is already doing some work in post-mortem brain, as are some of the other current programs. Dr. Chesselet elaborated that she was suggesting that post-mortem brain could be used to validate some of the findings from the animal model studies. Dr. Lisa Chadwick (on the telephone), one of the program directors of the NIH Epigenomics Roadmap Program who is specifically in charge of the Epigenomics of Human Health and Disease RFA, said that there are researchers funded under that program who are investigating the very question raised by Dr. Chesselet.

Dr. Cheung was the second Council reviewer. She agreed that the concept represents a very timely and comprehensive plan. She particularly liked the plan to integrate the genome, epigenome and transcriptome, and recommended including proteomics. She noted that in cells, all of those elements are working together, and that it’s a good idea to integrate exposure as a model to start. She asked how the findings from animal systems would be translated into humans. She expressed two concerns. She was opposed, she said, to separating the analysis from the data collection, and wondered how integration of existing data would lead to mechanistic understanding.

Dr. Tyson said it was recognized that each of the TaRGET activities would have to have a data analysis component built in, but that doing the data analysis separately was based on successful existing practices, such as with the NIH Epigenomics Roadmap.

Dr. Lloyd asked whether data from the NIEHS GuLF Study might be available to be integrated into this effort. He also asked whether the NTP might also be thinking about similar analyses, or might become involved in the TaRGET initiative. Dr. Bucher said that such efforts are already going on, and it is hoped that a tool can be developed to allow mining of the NTP Archives for epigenetic analysis.

Regarding brain epigenetics, Dr. Hu said that the epigenome-wide differences appear to be subtle, and that one of the biggest criticisms is cell type specificity, including cell type sorting techniques. He asked whether the existing working group has addressed that issue. Dr. Tyson said that the heterogeneity of brain tissues is not something that has been successfully addressed yet. Dr. Cheung said that the subtle differences are really important, and that that is an issue that should be pursued in the research. Dr. Tyson suggested that one way to do that would be by looking at chromatin states, which would yield signatures specific to specific cell types.

Dr. Postlethwait asked how the program would deal with the issue of environmental exposures producing a plethora of pathogenic effects in terms of disease causality versus more correlative associations. Dr. Tyson replied that one of the goals of the program would be to look at functional readouts, to go beyond correlative associations, and to be linked to either pathway disturbances or disease outcomes. Dr. McAllister addressed the ongoing issue of reverse causality, and said that that was one of the reasons for TaRGET II – to pay attention to windows of susceptibility and timing of epigenomic changes. She acknowledged that it is still an issue to be grappled with, but said that the mouse studies should help.

Dr. Lee asked about overlap with the SIEE. Dr. Collman said this concept would be a Special Solicitation, and so NIEHS would be responsible for the peer review.

Dr. Chesselet moved to approve the concept. Dr. Cheung seconded. Council voted unanimously to approve the concept.

VII. Concept Discussion: Role of the Environment in the Development of Autoimmune Disease

Health Science Administrator, Dr. Michael Humble from the Cellular, Organs and Systems Pathobiology Branch, presented to Council the Concept proposal to develop funding announcements that will examine the role of the environment in the development of autoimmune disease.

He briefly summarized the concepts of autoimmunity and autoimmune disease. He cited Type 1 diabetes, rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus as well-known examples of autoimmune diseases, and noted that collectively an estimated 23.5 million Americans suffer from an autoimmune disease, with considerable social and financial burdens as a result.

Genetics only account for roughly one-third of the incidence of autoimmune disease, which supports the idea that the etiology of autoimmune disease involves both genetic

and environmental factors. He cited several factors that support the role of environmental exposures in the development of autoimmune disease, including research involving dechallenge, rechallenge, geographic clustering, environmental response genes, strong biologic plausibility from *in vitro* data and animal models, and epidemiologic associations. He also briefly summarized the current NIEHS research portfolio related to autoimmune disease, including various toxicants and disease endpoints.

To assess the strength of the evidence for the role of environmental exposures in autoimmune disease, NIEHS, in conjunction with the American Autoimmune Related Diseases Association (AARDA), held an expert panel workshop in RTP in September, 2010. The goal of the workshop was to bring together experts from the EHS and autoimmune research communities to review the findings from their diverse research disciplines, identify conclusions that could be drawn from existing data, identify knowledge gaps and areas of uncertainty, and establish key elements of a coherent research agenda to help fill those gaps and resolve uncertainties. Dr. Humble summarized the evidence identified in the workshop from animal models, mechanisms, and epidemiology lending a high degree of confidence about the role of environmental exposures. He added that although there are areas of confidence, the workshop found that there remain many aspects in which data are lacking. Thus, it is proposed that one or more Funding Opportunity Announcement (FOAs) be developed to enhance the visibility of the NIEHS interests in the field and to stimulate research efforts that explore the role of the environment in the development of autoimmunity and autoimmune disease.

Relevant topics of research would include (but are not limited to):

Mechanisms

- Research efforts are needed to further clarify and/or elucidate the role of specific mechanisms in the development of environmentally induced autoimmunity and autoimmune disease. These could include:
 - sex-specific changes in immune function
 - determining the contributions of the various B cells subtypes in autoimmune disease and the role environmental factors have in biasing the activation of B cell subsets
 - examinations of specific chemical or physical agents capable of modulating regulatory T-cells (Tregs) and Th17 T-cells.

Animal Models

- Specific improvements to animal studies are needed, including use of disease markers from easily obtained biological fluids (e.g., blood) to enhance comparisons with human studies.
- In spontaneous disease models, studies should consider whether environmental exposures exacerbate or accelerate idiopathic autoimmunity, or reflect specific “environmentally associated” forms of autoimmunity.
- Screening for environment-associated effects should be conducted in both autoimmune prone and non-autoimmune prone models.

Epidemiology/Human Studies

- There exists a continuing need to identify single causal agents associated with the development of autoimmunity and autoimmune disease (e.g., specific solvents or pesticides contributing to increased risk for the group), as well as the need to address the role of multiple exposures.
- Studies of environmental exposure risks within specific autoimmune phenotypes are needed to elucidate associations which may be specific to that phenotype
- Defining critical windows in the timing of exposures and latencies relating to age, developmental state and hormonal changes

Dr. Humble concluded, “The idea is to stimulate this field, to enhance our research portfolio, and to raise our visibility in this area.”

Dr. Cheung was the first Council reviewer. She said she was very enthusiastic about the project. She noted that relative to other common diseases, the treatment of autoimmune diseases is “pretty poor,” and that there would be much to be gained from better understanding of mechanisms. Also, although they are complex, they are not as complex as some other common diseases such as schizophrenia, and there are easily accessible cell types, allowing acquisition of sufficient tissue for mechanistic study. She approved of the proposal’s focus on disease mechanisms using both humans and animal models. She recommended addressing the molecular effects of how different exposures lead to different types of autoimmunity. She noted that by understanding mechanisms, there could be new opportunities for intervention, whether through treatment or prevention of exposures.

Dr. Conti was the second Council reviewer. She noted that the concept would fit well with each of the Strategic Goals included in the new NIEHS Strategic Plan. She mentioned that companion animals suffer from the same array of autoimmune diseases, and that advances in understanding would benefit them as well. “I think this opportunity

for having the research bridge the epi and immunology and toxicology is too juicy to pass up," she added.

Dr. Taylor asked whether Dr. Miller had talked about the topic at the last Council meeting, and asked for his comments. Dr. Miller confirmed that he had given an overview of autoimmune diseases at the previous meeting. He noted that the autoimmune diseases are all increasing in prevalence, lending urgency to the need to learn more about them and possibly prevent them in the future.

Dr. Hu inquired how the proposal is viewed at NIAID, and at what level there might be opportunity for synergy or coordination, since autoimmune disease would be part of its purview. Dr. Birnbaum said she had spoken to NIAID director Dr. Fauci, and that they are not very interested in the environmental component and are happy to let NIEHS pursue that line of inquiry. Dr. Collman added that there is a research portfolio at NIAMS, and Dr. Humble has been in contact with its program director regarding shared interests. Dr. Maddox added that the Office of Research on Women's Health would also be quite interested, as it fits within one of its strategic goals. She said it is intriguing and interesting to look at chronic diseases with a significant environmental element in addition to genetics.

Dr. Orme-Zavaleta asked whether lifestyle or other types of social sciences such as environmental justice considerations would be included. Dr. Humble said that those elements would not be ruled out at this point, and that it still needed to be determined how broad or how narrow the concept should be. Dr. Collman pointed out that there have been environmental justice grants in the past looking at lupus in communities, so there is precedent in the NIEHS portfolio.

Dr. Cheung moved to approve the concept; Dr. Conti seconded. Council voted unanimously in favor of the concept.

VIII. Developing Improved Methods to Measure Human DNA Repair Capacity

Dr. Leona Samson from the Center for Environmental Health Sciences at MIT briefed Council on her group's efforts to refine measures of human DNA repair capacity. She began her talk by describing different types of DNA damage and the different biological repair strategies that specifically address them. From that context, she discussed how using the host cells' ability to reactivate the expression of a reporter gene in a repair-dependent manner is the basis of her new system for measuring DNA repair capacity, which is capable of tracking multiple DNA repair pathways simultaneously with an easy to read output. Instead of using a single reporter as past systems have done, Samson's system uses different shades of fluorescent proteins. This allows researchers in her lab

to monitor a variety of pathways simultaneously with a simple fluorescent light detector. Using that system, her group has been able to evaluate DNA repair systems including nucleotide excision repair, homologous recombination, mismatch repair and MGMT direct reversal repair. The repair capacity reporting plasmids could also potentially be used in cell lines derived from patients, which would allow determination of a person's DNA repair capacities and deficiencies for specific types of damage. Dr. Samson said she is now looking to use her fluorescent reporter system as a guide to direct more detailed studies of other kinds of DNA damage that do not inhibit transcription.

IX. The Consequences of DNA Replication Infidelity to Human Health

Dr. Thomas Kunkel, leader of the NIEHS DNA Replication Fidelity Group, provided Council an overview of the consequences of DNA replication infidelity to human health. He began his talk with a metaphor for the impressive biology that lets healthy people avoid replication errors. Imagine, he said, typing 2,000 copies of a lengthy textbook with no mistakes between 8 a.m. and 4 p.m. If that text book was the human genome, the workday would represent the 8 hours of the S phase of DNA replication. Of course, much like a typist, the DNA replication machinery relies on its versions of the backspace function, exonuclease activity, and spellcheck, mismatch repair, as well as hitting the right keys, nucleotide selectivity. He went on to explain the importance of the complex interaction between the polymerase making the new DNA strand and each incoming nucleotide that would be added, describing the different polymerases important for proper replication. After describing the scrupulous fidelity of most DNA replication polymerases, Dr. Kunkel introduced the translesion synthesis (TLS) polymerases, which are less picky and more flexible in their active sites, allowing them to replicate damaged DNA. This allows TLS polymerases to correct lesions. These more liberal polymerases also allow errors when mutagenesis is beneficial, such as during antibody production. In this manner, TLS polymerases make the new DNA more as it should be by allowing it to be less like its template. He also spoke about another type of mistake during replication — the insertion of RNA bases into a new strand of DNA. Ribonucleotides contain an extra oxygen atom that can result in strand cleavage and genome instability, and the incorporation of ribonucleotides leads to damage-susceptible DNA. His research suggests that there may be a signaling function behind ribonucleotide incorporation.

X. NIH Budget Process

Laurie Johnson, chief of the NIEHS Financial Management Branch, provided Council with a primer on the NIH budget process – “Budget 101.”

She described how the fiscal year budget process, comprised of three phases, formulation, justification and execution, crossed multiple calendar years. She depicted what the appropriation process is supposed to look like, starting in March with formulation, through January of the following year with the President's budget. In February, the Congressional Justification, the detailed budget request, is presented to Congress, followed by hearings and Congressional actions. By October 1, an appropriation should have been passed by Congress and signed by the President. However, this does not happen often and usually the execution phase begins with a Continuing Resolution (CR) providing operating funds for a specified length of time. This results in considerable effort to ensure that proper authority is in place and that each division knows what it can spend. Long-lasting CRs can be particularly troublesome, because they prolong uncertainty about the full-year spending level. It is almost certain that FY2013 will begin under a CR, at least through the election. NIEHS/NTP receives funding from more than one appropriation, which can increase operational challenges. Ms. Johnson showed Council the NIEHS census count as of June 30, 2011. The census is used as the basis for allocating many NIH shared costs to the institutes. As of that date, the NIEHS census totaled 1,420 people.

She provided more details about each of the three phases of the budget process. In the formulation phase, the steps are:

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| • With IC Input, NIH Director Identifies Philosophy & Priorities | Mar-May |
| • ICs Prepare RPG Commitment Base Following Policy Guidance | Mar-Apr |
| • NIH Directors' Budget Retreat | May |
| • NIH Preliminary Budget to HHS | May-Jul |
| • NIH Budget Submission to OMB | Aug-Sept |
| • OMB Confidential Passback and Appeals | Nov-Dec |
| • Develop President's Budget (PB) &
Prepare Congressional Justification in Accordance with
NIH Guidance and Administration Policies | Dec-Jan |

In the presentation or Congressional phase, the steps are:

- | | |
|--|-----------|
| • Congressional Justification Presented to Congress | February |
| • Congress Passes Budget Resolution | April |
| • Congressional Hearings before House and Senate
Appropriation Subcommittees | Spring |
| • House and Senate Appropriations Subcommittees
Markup the President's Budget | Summer |
| • Full Committees, Full House/Senate Action | |
| • Conference to Resolve Differences | July-Aug |
| • Bill to President | Sept-Dec |
| • Appropriation (or CR) | October 1 |

In the execution phase, the steps are:

- Fiscal Year Begins October 1
- Funding Authority Levels Established
 Within NIH Business System Early Oct
- NIH Develops Operating Policies Within
 Congressional Parameters Oct-Dec
- Obligation and Expenditure of Appropriated Funds Oct-Sept
- Reallocation Notification (if needed) May-June
- End of Fiscal Year, Books Closed Sept 30
- Reconciliation Oct-Nov
- Collect and Report Official Data, Including
 Financial Reports and Research, Condition,
 and Disease Categorization (RCDC) Dec-Jan

She depicted appropriations from FY 2009 through FY 2012, along with the FY 2013 President's Budget request. The NIEHS request is \$684 million; Superfund is \$78.9 million, and we anticipate a budget pass-through of \$10 million from DOE for worker training, as has been the case in the past. She showed a bar graph depicting the history of NIEHS appropriations, which portrayed the last three years as having been flat. Another bar graph broke down the various NIH appropriations, with NIEHS falling roughly in the middle amongst the ICs.

NIEHS money comes mainly from the Labor/HHS appropriation and Interior/Environment appropriation. Other money comes from the NIH Common Fund, and small amounts come from a variety of other sources.

Ms. Johnson presented a pie chart depicting where the money that comes to NIEHS goes. Of the \$763 million obligated in 2011, \$263 million went to RPGs, \$148 million to R&D contracts, \$185 million to intramural research, and \$79 million to Superfund research, with smaller amounts devoted to centers, other grants, research training, and research management and support. She also showed a mechanism table, which Congress finds useful to assess spending, depicting different types of research project grants, and other grant activities, adding up to nearly \$308 million in research grants. Other mechanisms such as research training, R&D contracts, intramural research, and research management and support, along with Superfund, made up the remainder of the nearly \$763 million total expenditure. She also presented data comparing spending mechanism proportions between NIH and NIEHS. NIEHS had proportionately less RPG spending than NIH, but more R&D contracts (largely due to NTP) and intramural research spending.

Dr. Cheung noticed that the \$10 million training pass-through was not shown under the President's 2013 budget. Ms. Johnson said that that money actually comes to NIEHS from an agreement with the Department of Energy, and so is not part of the NIEHS

budget. Dr. Birnbaum noted that the appropriation also comes from a different subcommittee. Dr. Cheung asked if that funding was earmarked specifically or could be used for other training purposes. Ms. Johnson said that it is specifically designated to be passed to the NIEHS Worker Training program.

XI. Report of the Deputy Director, NIH Office of Extramural Research

Dr. Sally Rockey, NIH Deputy Director for Extramural Research, provided Council with an NIH update titled "Interesting Times, Challenging Times." Her presentation consisted of a description of the procedures and strategies in place and being contemplated for managing NIH research budgets in austere times, as well as NIH efforts in the biomedical workforce area. She said that Working Groups on diversity and information technology would be reporting in June at the meeting of the Advisory Committee to the Director.

Looking at the NIH budget since 1998, she noted its doubling in the 1998-2003 period, and the fact that it has remained basically flat in the years since. However, based on buying power calculations, the doubling has been undone. She said it has been difficult to deal with a flat budget while still accommodating the increasing cost of research. She described the 2-year ARRA funding, which supported "some great science," with the added benefit that it was predictable.

She said that one of the elements impacted by managing a flat budget is success rates. With a rising number of applications but a static number of awards, there is a lower success rate – it is currently roughly 18%. She said that is distressing, because "so much good science gets left on the table when you have such low success rates."

Looking at this year's budget request, the FY2013 President's Budget Request, NIH is flat compared to FY2012 - \$30.86 billion. She said that considering the tough budgetary times, having a flat budget proposal "was actually a win for us." She mentioned that the first and only budget cut in the 125 years of NIH occurred in 2011. The Office of Management and Budget (OMB) asked that the number of Research Project Grants (RPGs) be kept steady or increased, which puts pressure, she said, on all of the commitments made in the past. OMB also asked NIH to ramp up the Cures Acceleration Network by \$40 million, as part of the new NCATS initiative, and to provide \$80 million in additional support for Alzheimer's disease research from the Public Health and Prevention Fund as part of an HHS-wide initiative.

To keep competing awards at a constant level, OMB suggested that NIH reduce non-competing RPGs by 1%, avoid growth in the average size of competing awards, and eliminate inflationary increases in out-year budgets of both competing and non-

competing RPGs. Also, NIH is instituting a new policy (as described in detail by Dr. Collman in her presentation) that applications from PIs who already receive in excess of \$1.5 million per year in total costs be given additional scrutiny and review by the Advisory Council of the IC to which the application is assignment. She stressed that it is not a cap, but simply additional scrutiny of highly-funded PIs. OMB also suggested that NIH continue its policy of funding applications from early-stage investigators at the same success rate as established investigators for new R01 equivalent applications.

Dr. Rockey presented a series of options for managing NIH resources:

- **Current Way of Managing**
 - Bottom out success rates (doing nothing but letting the system correct itself)
- **Other Options**
 - Reducing or limiting size of awards
 - Limiting number of awards held by a PI
 - Limiting the amount of funds a PI can hold
 - Limiting salaries of PIs

She said that on average, PIs have roughly 1.4 awards, dispelling the myth that there are many who have far more. The top 20% of individual PIs receives about 50% of NIH funds. They tend to have larger awards, and they do tend to have 2-3 awards. She noted that the data show that very few individual have more than 4 awards. Ten percent of funded institutions (120) receive 80% of the funds, with 50 receiving 70%. They are generally the medical schools, where much biomedical research is conducted.

The current way of managing is generally project-based, with competitive peer review yielding on average \$414,000 per year for 4.4 years. If no action was taken, the Darwinian, survival of the fittest approach would remain, with the likelihood that success rates would continue to fall. This would also result in a risk of reduced emphasis on innovation as applicants “play it safe” to get through peer review.

She said that in these tough times, it is more important than ever that ICs, as they evaluate and rearrange their research portfolios, focus on their scientific priorities. NIH has been conducting a rigorous evaluation of the entire research portfolio, resetting priorities in a focused, intentional way. This is intended to eliminate duplications and reduce support for less innovative research while increasing support for highly innovative research.

She noted that NIH funding is approximately 85% intended to support the people involved in the research. With that in mind, she presented examples of the impact of reducing the average size of an award. An award reduction of \$25,000, for example,

would have a minimal impact on success rates and number of awards, but would have real negative consequences on the individuals involved.

She depicted the impact of limiting the number of awards per PI. Limiting to 5 RPGs per PI would only result in an additional 15 RPGs. Limiting to 3 would still only add 264 RPGs. Limiting to 2 RPGs per PI, which would be quite Draconian, would only add 964 awards. Thus, limiting the number of awards per PI does not seem like a viable option.

Limiting the total amount of funds per PI would have a substantial impact. She presented the examples of \$1 million, \$800,000, and \$400,000 limits. Limiting funding to \$1 million would affect 3,245 PIs, yielding a saving of \$3.1 billion, which would allow approximately 2,000 additional competing RPG awards at an average of \$400,000. Limiting funding to \$800,000 would affect 4,629 PIs, yielding a saving of \$3.9 billion, allowing 2,400 additional RPGs. Limiting funding to \$400,000 would affect 12,000 PIs, yielding a saving of \$7.1 billion, allowing 4,400 additional RPGs. She pointed out that the drawback to these ideas is the fact that NIH is a meritocracy, with the belief that the best science should be funded regardless of whom is doing it. Thus, this would be a very different mindset for how science is supported in the US.

To depict the option of limiting salaries, Dr. Rockey presented data on combined percent effort. She said that philosophically NIH has built a record of providing strong support for PI salaries, and that any change would need to be "a long, long-term solution." She described a sudden change to the salary structure that took place this year, as Congress limited the rate at which an individual can charge their salary from Executive Level 1 (\$199,000) to Executive Level 2 (\$179,000). Many universities had to make up the funds overnight to make up for the reductions, with dramatic impact.

Dr. Rockey described the establishment of the NIH Working Group to examine the future biomedical workforce, with the intent to develop a model for a sustainable and diverse US biomedical research workforce that can inform decisions about training and other elements for NIH. Based on a great deal of data collected over the past 25 years, the group will make recommendations for actions that NIH should take to support a future sustainable biomedical infrastructure.

She presented some of the current data regarding the NIH workforce. Approximately 70% of PIs are PhDs. The average age of first R01 awards to PIs with PhDs, MDs or MD-PhDs has gradually risen, to the early 40s at this point. This limits the attractiveness of the field to young students. She showed a time lapse of the average age of all investigators, which graphically depicted the aging of the workforce from 1980 to 2010. The data also depicted a growing gap between the times of gaining a first medical school faculty and a first R01. A chart showed a similar trend from 1980 to 2010 when tracking the percentage of R01 PIs age 36 and younger and age 66 and

older – the trend lines meet in 2002, and now the older PIs outnumber the younger ones. “So the workforce is aging... [which] reduces the opportunities for new investigators coming in,” she said.

Dr. Rockey depicted the trends in NIH training grants and fellowships, which have remained relatively stable over the years, even during the NIH doubling. The number of graduate students supported by NIH grants has risen, however, indicating that that is the preferred method of support at present. A similar trend has been seen with postdocs, including a significant influx of foreign researchers.

She presented data from an NSF 1993-2008 survey of US-trained doctorate recipients. The number of basic biomedical PhDs has skyrocketed over the last ten years, corresponding with the doubling of the NIH budget. She noted that the number of PhDs currently outstrips the number of jobs available, particularly in academia. She showed graphs depicting the role of tenure track and non-tenure track positions, with non-tenure track biomedical positions having grown substantially in recent years, while tenured positions have declined. However, since the survey data ends in 2008, it does not reflect the economic downturn from 2008 to the present, which has undoubtedly had an impact. Another graph showed the relationship between science and engineering PhD field and occupation, reflecting that there is some flow out of the biological/life sciences field. A chart of the relationship between life sciences PhD field and occupation showed that within life sciences, biological sciences have the highest number of PhDs working in a related occupation. However, the trend in each of the life sciences fields is for fewer PhDs remaining in their doctoral fields. Other data showed that over 70% of biomedical PhDs begin working in research occupations out of graduate school, and that 60% are still in research 11 years after receiving their degrees. That figure is also dropping over time, however.

Dr. Rockey noted that because of the extended training period, where biomedical students have long PhD periods and long postdocs, there is a negative impact on lifelong earning potential compared to other scientific fields and non-scientific fields. That affects the long-term attractiveness of the career. She said that accelerating the training process should be considered as a way to enhance the attractiveness of the field. The type of training should also be considered, because although 33% of PhDs go into academia currently, some 30% go into industry, 15% into government, and 15% go outside scientific pursuits. “We have to think about all of those opportunities that are offered to an individual during a training program to make our domestically trained scientists very competitive for the jobs that they’re going to get,” she said.

Aside from trends regarding the attractiveness of the field, diversity within the workforce remains a problem, as it has changed little over the past 25 years.

Dr. Rockey concluded her presentation by referring to the Office of Extramural Research website for grant information, and her blog, *Rock Talk*.

Dr. Gasiewicz asked whether Dr. Rockey had seen any trends in domestically trained PhDs taking jobs outside the US. She said that it's a very small amount, and not enough to change the scope of the workforce presently, despite efforts by some countries to encourage their US-trained postdocs to return to their home nations.

Dr. Lee asked if the data had been analyzed in terms of women. Dr. Rockey said there is much information on that at the website. She said that the proportion of women in graduate training is over 50% at this point, but not in the number of PIs. She said she hopes there will be a big influx over time as women progress from graduate training programs – “they should now become a bigger portion.” Analysis has shown that women are enjoying a roughly equal success rate in R01 awards, but that they are not coming back for renewals as often. That is partially due to their presence in clinical work, where renewals would not apply, but also they are not as successful as men in renewals, which Dr. Rockey said is not understood. Dr. Birnbaum mentioned that NIH has a committee on women in biomedical research careers, on which she serves, which looks at many of the issues being discussed, and that more information is available on the committee's website.

Dr. Lloyd asked whether Dr. Rockey's group had analyzed the potential impact of going from Executive Level 2 to 3 in NIH salary support, noting that his university had predicted that such a move would be exponentially more damaging than the recent change from Executive Level 1 to 2. Dr. Rockey agreed that the impact of dropping salary support to \$159,000 would be enormous, but said a formal analysis had not been conducted as yet. Dr. Lloyd wondered if perhaps the roll-back of PI salaries might make the most financial sense for NIH within the options being considered. Dr. Rockey said the community seems ready more than in the past to at least have a conversation about that concept, in that there is acceptance that a more sustainable model must be achieved. She said there would be differential impacts from such an action, which must be considered. “This is a huge shift,” she added, “and in order to change this world that we've created over the last 125 years...we have to take some time to be thoughtful about how we do it, and we have to do it with the community.”

Dr. Woychik asked about the possibility of capping indirect costs. Dr. Rockey said that is already happening with indirect costs in training grants to universities. She added that over the years, the overall NIH level of indirect costs has been constant, at 28%. She noted that there are “true direct costs and true indirect costs, and we need to be able to have institutions recover both.”

Dr. Chesselet said that although there could be a cap or decrease in salaries, benefit rates continue to climb, so there would be little overall effect. Dr. Rockey agreed that that is a problem. She noted that postdoc benefits are "all over the place," which is another element of the unattractiveness of being a postdoc.

Dr. Cheung asked whether a cap on the number of applications an individual could submit had been considered. Dr. Rockey said that idea has been on the table as well, but that much gamesmanship of PI status would take place if that was instituted.

Dr. Lee noted that her institution's tenure review committee takes an investigators number of grants into account as one marker of scholarship. Dr. Rockey agreed that the reward system in the biomedical world is largely built on ability to get NIH grants, and that given the way science is going, with many multi-PI grants and collaborations, institutions should re-think their reward systems. She added that there should be a provision to help postdocs who are considered going into industry rather than academia.

XII. NIEHS Neurodegeneration Research Portfolio 1986-2009

Dr. Kristi Pettibone from the DERT Program Analysis Branch briefed Council on a recent evaluation of the NIEHS neurodegeneration research portfolio from 1986-2009. She said that requests for funding related to neurodegeneration research are likely to come before Council within the next few meetings, so it is timely to provide Council with some background on the current portfolio and how it has grown over the last 25 years.

When NIEHS first funded a neurodegeneration grant in 1986, it was not regarded to be the start of a program. It has evolved into a specific program area, however, and in 2009 there were more than 70 grants.

The portfolio evaluation began in Spring 2010, with the report written in Summer 2011. Since then, PAB and program staff have worked to disseminate and utilize the findings.

In the 1986-2009 portfolio timeframe, there were 147 grants to 118 researchers. Funding has grown concomitantly with the number of grants, with some extra funding in 2009 due to ARRA. The dollar amount is approximately \$25 million, or roughly 7% of the NIEHS budget.

The Program Analysis Branch used a logic model to direct the evaluation. The logic model includes inputs and project resources, activities, outputs, and short- and long-term impacts. Dr. Pettibone displayed a graphic based on the four elements of the logic model that depicted the various analyses of the neurodegeneration portfolio. The characteristics of the portfolio were also assessed, including solicited vs. unsolicited grants, grant mechanisms, type of science, and diseases and exposures. Portfolio

funding was split roughly evenly between solicited and unsolicited grants. The first solicited grants were issued in the late 1990s, and grew over time. Unsolicited grants grew substantially in the 2004-2005 period, and have continued to grow since then. Approximately 80% of the portfolio is funded through R mechanisms, with almost half of the portfolio funded through R01s. K and F career development grants make up about 15%, while P and U grants comprise the remaining 5%.

The neurodegeneration research is primarily basic – 108 of the 147 grants, with applied research accounting for the other 39 grants. Dr. Pettibone elaborated that the focus of the research tends to be documenting the role of the environment in the development of neurodegenerative diseases. Diseases addressed were led by Parkinson's Disease with 116 grants, followed by Alzheimer's with 22, ALS with 18, Huntington with 2 and Konzo with 1 (grants can address multiple diseases). Parkinson's has been the focus because of the robust evidence of a link between the disease and environmental exposures. In terms of exposures addressed, the breakdown is metals (manganese 22 grants, heavy metals in general 17) and pesticides (general 26, paraquat 16, rotenone 9, organochlorines 9).

In analyzing the output of the portfolio, the focus tends to be on publications by the grantees along with training and retention of researchers in the neurodegeneration science area. The portfolio had produced 1219 publications, with the larger grants awards and longer grant awards tending to have more publications. The number of publications from the solicited and unsolicited grants was similar, but the impact factor associated with the solicited grants was higher than the unsolicited (4.6 vs. 3.1). Citations were substantially higher among the solicited grants publications (21.1 vs. 8.4). Applied research grants had slightly more publications than basic research grants (11.7 vs. 8.7), but basic publications had slightly more citations (15.4 vs. 13.6). In terms of training and capacity, of the 118 funded researchers, 53 (45%) were still conducting NIEHS-funded neurodegeneration research in 2010, 29 (25%) had more than one neurodegeneration grant, and 9 (7%) were still conducting research with NIEHS funding but were not currently conducting neurodegeneration research. These figures indicated that there was much success in retaining neurodegeneration researchers.

In terms of impacts, neurodegeneration researchers made several key contributions to the field. They have rejuvenated interest and research on neurodegenerative diseases, established the linkage between environmental exposures and neurodegenerative diseases and have helped to sustain research capacity in developing countries. The neurodegeneration researchers have provided the strongest evidence to date that links environmental exposures to pesticides with Parkinson's Disease (PD), along with the interaction between genetic and environmental risks of PD, and the role of combined exposures in PD risk. Mechanistic studies in multiple model systems have also provided biological plausibility for a causal role played by exposures.

Researchers have also made significant contributions in ALS research, including the development of protein biomarkers to facilitate more rapid diagnosis, as well as to research in new modalities for treatment of the disease.

The researchers are also exploring whether environmental exposures can accelerate the development of neurodegenerative diseases, and whether combined exposures affect disease progression.

The evaluation also found that there was a third type of application, which they called a “quasi-solicited” award, comprised of applications to broad RFAs such as ViCTER and ONES, which could encompass neurodegeneration research. They found a number of neurodegeneration grants that had been funded under these broad RFAs, demonstrating the maturity of the field, the quality of the applications, and the retention of the researchers. Other benefits of the neurodegeneration program included graduate training opportunities from Center grants, as well as interdisciplinary research opportunities.

Future plans associated with the logic model analysis will involve development of new tools that will allow reading of grantees’ publications and progress reports, to allow more detailed assessment of their impact on the field. Portfolio evaluation findings will be incorporated into future program planning, including connecting neurodegeneration research to strategic plan goals. The findings will be widely disseminated, including website content, EHP commentary, fact sheets, a review paper, and at an upcoming neurodegeneration meeting with DOD.

Dr. Birnbaum praised the “superb” work of the Program Analysis Branch.

Dr. Hu asked whether the portfolio included research on precursors of Alzheimer's disease. Dr. Lawler replied that studies in that area were coded and included as part of the portfolio. She said there were a few such studies.

Dr. LeMasters suggested that the logic model approach be used in the preparation of future concept documents to be presented to Council.

Dr. Maddox asked whether the portfolio included research on the impact of the environment on intellectual and developmental disabilities, with a focus on Down syndrome. Dr. Gray from the Susceptibility & Population Health Branch noted that those types of studies were in her area, within the neurodevelopment and neurodevelopmental delays, and were not included in neurodegeneration portfolio analysis.

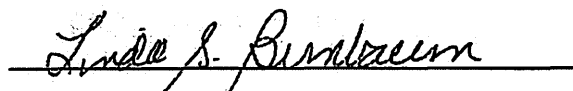
XIII. Consideration of Grant Applications

This portion of the meeting was closed to the public in accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

XIV. Adjournment

The meeting was officially adjourned at 12:30 pm on May 23, 2012.

CERTIFICATION:



Linda S. Birnbaum, PhD, DABT, ATS
Chairperson
National Advisory Environmental
Health Sciences Council



Gwen W. Collman, PhD
Designated Federal Official
National Advisory Environmental
Health Sciences Council

Attachment:
Council Roster