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

MINUTES OF THE NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

February 16-17, 2011

The National Advisory Environmental Health Sciences Council convened its one hundred thirty-second regular meeting on February 16, 2011 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 February 16, 2011 from 8:30 a.m. to 2:30 p.m. and on February 17, 2011 from 8:30 a.m. to 3:30 p.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 February 16, 2011 from 3:00 p.m. to 5:00 p.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*.

Council Members Present

Stephen Baylin, MD
Chris Bradfield, PhD
Julia Brody, PhD
Hillary Carpenter, PhD
Steve Dearwent, PhD
Robert Dyer, PhD
Richard Finnell, PhD
Thomas Gasiewicz, PhD
Andrea Hricko, MPH
Mary M. Lee, MD
Grace LeMasters, PhD
George Liekauf, PhD
R. Stephen Lloyd, PhD
Thomas McKone, PhD
Sem Phan, MD, PhD
Kenneth Ramos, PhD
Jerald Schnoor, PhD
Palmer Taylor, PhD
Deborah Winn, PhD
Nsedu Obot Witherspoon, MPH

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NIEHS Staff

Joel Abramowitz, PhD
Kathy Ahlmark
Janice Allen, PhD
Beth Anderson
David Armstrong, PhD
John Balbus, MD, MPH
Eddy Ball, PhD
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard
Linda Birnbaum, PhD, DABT, ATS
Wanda Boggs
John Bucher, PhD
Janet Cakir
Danielle Carlin, PhD
Jennifer Collins
Gwen Collman, PhD
Helena Davis

Caroline Dilworth, PhD
Christina Drew, PhD
Serena Dudek, PhD
Dorothy Duke
Sally Eckert-Tilotta, PhD
Lisa Edwards
Benny Encarnacion
Christine Flowers
Mary Gant
Barbara Gittleman
Kimberly Gray, PhD
Astrid Haugen
Jerry Heindel, PhD
Heather Henry, PhD
Michael Humble, PhD
Laurie Johnson
Paul Jung, MD, MPH
Annette Kirshner, PhD
Cindy Lawler, PhD
Chris Long
Robin Mackar
J. Patrick Mastin, PhD
Elizabeth Maull, PhD
Michelle Mayo
Kimberly McAllister, PhD
Liz McNair
Aubrey Miller, MD MPH
David Miller, PhD
Ellen Moul
Sri Nadadur, PhD
Sheila Newton, PhD
Aaron Nicholas
Heather Nicholas
Liam O'Fallon
Ted Outwater
Michelle Owens
Kristi Pettibone, PhD
Jerry Phelps
Nancy Powell
Leslie Reinlib, PhD
Margarita Roque
Elizabeth Ruben
William Schrader, PhD
Thad Schug, PhD
Andrew Seipel, PhD
Daniel Shaughnessy, PhD

Carol Shreffler, PhD
William A. Suk, PhD, MPH
Christina Teng, PhD
Kimberly Thigpen Tart, JD
Claudia Thompson, PhD
Frederick Tyson, PhD
Michelle Victalino
Chris Weis, PhD
James Williams
Mary Wolfe, PhD
Leroy Worth, PhD
Rick Woychik, PhD
Darryl Zeldin, MD

Members of the Public Present

David Brown, SRI
Charles B. Gause, Luna Innovations
Ernie Hood (Scribe)
Mike Phillips, RTI International
Branka Sekis, Social and Scientific Systems, Inc
Pamela Schwingl, PhD, Social and Scientific Systems, Inc.

I. Call to Order and Opening Remarks

Dr. Linda Birnbaum, Director of NIEHS and NTP, welcomed attendees and called the meeting to order. She welcomed new Council member Dr. Tom McKone and *ex officio* members Dr. Steve Dearwent, Dr. Robert Dyer, and Dr. Deborah Winn. She thanked retiring NAEHSC members Dr. Hillary Carpenter, Dr. George Liekauf, and Dr. Kenneth Ramos for their service. 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 September 2010 Meeting Minutes

Approval of the September 2010 minutes was moved and seconded, and Council voted unanimously to approve the minutes. Dr. Collman also noted the dates of the upcoming Council meetings for members to put on their calendars.

IV. Report of the Director, NIEHS

Noting that all Council members were present for this meeting, Dr. Birnbaum updated them on staff changes. Dr. Rick Woychik has assumed the role of Deputy Director of NIEHS. Dr. Gwen Collman has been appointed to be permanent Director of the Division of Extramural Research and Training. Searches are still underway for a Scientific Director, Clinical Director, and Associate Director for Management.

Dr. Birnbaum updated Council on potential appropriations for NIEHS, NTP, Superfund, and NIEHS/Department of Energy training. She reminded Council that the FY 2010 appropriation for NIEHS was more than $689 million, and that number remains in force as the federal budget is presently under a Continuing Resolution. Dr. Birnbaum also stated that although the exact numbers are not yet known, the House budget bill (H.R. 1) would return NIEHS to approximately an FY 2008 spending level of $653 million. The President's budget request for NIEHS for FY 2011 is basically flat, which she said "is looking better all the time." The upcoming situation is very uncertain, she said, with the most likely scenario being a series of Continuing Resolutions.

The situation with the Superfund budget is equally uncertain at present, as is the overall NIH budget, although there is some speculation that NIH could face a cut of up to $1 billion.

Dr. Birnbaum provided Council with updates on highlights in the Institute since the September Council meeting. She told members that work is continuing regarding the Gulf oil spill. Preparation continues for the Gulf Longitudinal Follow-up Study (GuLF), which will study the long-term health effects of the oil spill. Field work will begin in March. The study is projected to cost $34 million over its first five years. In addition to the GuLF study, the NTP is still involved with toxicology research on the spilled oil and the dispersants used in clean-up efforts. Funding for research consortia related to the oil spill is also continuing, going to investigators in the Gulf states and incorporating community participation. Three to five consortia are expected to be formed, and they should be funded by June 30. NIEHS is also funding individual research grants related to the oil spill, for research and outreach efforts on the health effects of exposure to oil and dispersants. Also, the Worker Education and Training Program (WETP) has awarded five grants to the Gulf region for ongoing health and safety training projects.

Aside from Gulf region activities, the WETP has had an active year, with the Hazardous Waste Worker Training Program awarding $20.6 million to 20 organizations, the Nuclear Weapons Cleanup Training Program awarding $9.6 million to eight organizations, the Minority Worker Training Program awarding $3.5 million to four organizations, and the Hazmat Disaster Preparedness Training Program awarding $2.3 million to ten organizations.

Environmental justice has continued to be an area of focus for the Institute, with community forums in Kentucky and New Orleans, a Keystone Lecture last October, sponsored sessions at the American Public Health Association's annual meeting in late 2010 and participation in a White House Environmental Justice Forum among the recent highlights.

Dr. Birnbaum updated Council on developments at the Clinical Research Unit. She said that about 35-40 subjects per week are coming to the clinic to participate in approximately 15 ongoing studies.

There have been a variety of workshops, meetings and conferences since September 2010, including an Expert Panel Workshop on the environment and autoimmune disease, the inaugural meeting of the Interagency Breast Cancer and Environmental Research Coordinating Committee, the launch of the Global Alliance for Clean Cookstoves, and a conference on Health Consequences from Xenobiotic-Gut Microbiome-Host Interactions. An NIEHS scientist, Dr. Darlene Dixon, co-chaired the 3rd International Congress on Advances in Uterine Leiomyoma Research at the Institute, examining the state of the art in research on uterine fibroids. Other recent workshops have included an Autism and the Environment conference, a WETP fall awardee and technical meeting, a meeting of the NIEHS Centers for Nanotechnology Health Implications Research Consortium, a meeting of DISCOVER grantees on "Translation and Beyond," and an NIEHS Workshop on Air Pollution and Brain Health.

In January, a major, three-day NTP Workshop was held in Raleigh, entitled "Role of Environmental Chemicals in the Development of Diabetes and Obesity," which consolidated the recent scientific findings in that emerging area of research. In January, ICCVAM also held two workshops on best practices for regulatory safety testing, including those for chemically-induced eye injuries and for chemically induced contact dermatitis.

Relating recent Institute highlights in translation and communication, Dr Birnbaum cited a 10-minute film put out by the Superfund, "In Small Doses: Arsenic." She also described the Climate Change and Human Health white paper released in 2010, and the Partnerships in Environmental Public Health (PEPH) Metrics manual, which was recently released for comment.

Dr. Birnbaum updated Council on several awards won in recent months by NIEHS personnel, including her own election to the Institute of Medicine, a Lifetime Achievement Award from her *alma mater*, the University of Illinois at Urbana-Champaign, and delivering the James L. Whittenberger Lecture at the Harvard University School of Public Health.

She also shared the awards given to intramural scientists at the Science Awards Day ceremony in November. Recipients included Scientist of the Year to Dr. Dale Sandler, the first epidemiologist and the first woman to receive that honor.

Dr. Birnbaum updated Council on several recent scientific advances marked by NIEHS and NTP personnel and extramural grantees. They included:

- Effects of Pausing of RNA Polymerase II
- Environmental Alterations to Genetic Networks
- Chemical Effects on Gene Expression in the Thymus
- Epigenetic Silencing in Lung Cancer
- Releasing the Brake on Synaptic Plasticity
- Mitochondrial Dysfunction in Autism
- Tissue Burden of Chromium in Rodents from Drinking Water Exposure
- Profiling DNA Methylation and Identification of Monoallelic Epigenetic Modifications
- New Exposure Paradigm (the "exposome")

Dr. Birnbaum summarized testimony she had delivered recently. In September 2010, she appeared before the Senate Committee on Veteran's Affairs, testifying on the science behind the Institute of Medicine's 2008 pronouncement regarding an association between exposure to Agent Orange and ischemic heart disease. That same month, she also spoke at a Congressional Briefing on endocrine disruptors. In February 2011, she testified before the Senate Committee on Environment and Public Works hearing on drinking water contaminants, particularly perchlorate, CrVI, and TCE.

She related NIH Building 1 developments, noting that Dr. Kathy Hudson has been named Deputy Director for Science, Outreach, and Policy, and that Neil K. Shapiro, JD, MBA, has been named Associate Director of the Office of the Budget.

She concluded her presentation by briefly discussing the potential that there may be changes in the NIH ICs, as per the Scientific Management Review Board (SMRB), which provides advice to the Director. Among the recommended changes made by SMRB Working Groups are the creation of a new institute to focus on substance use, abuse, and addiction and a new institute devoted to translational medicine and therapeutics.

Regarding the potential new institute on substance abuse, Ms. Hricko asked if NIEHS was currently funding any research in that area. Dr. Sheila Newton replied that NIEHS currently has approximately $4.6 million of research in the substance abuse category, including small projects on alcohol toxicity, opiates, and tobacco. Dr. Birnbaum added that the NIH Research, Condition, and Disease Categorization (RCDC) reporting

system has distinct category requirements, which environmental health projects sometimes do not fit well.

V. Strategic Plan Process

Dr. Rick Woychik, the new Deputy Director of NIEHS, briefed Council on plans for formulation and implementation of a new strategic plan (SP) for the Institute, which will cover the years 2012-2016. He said that the process is slated to take 15 months, which will be marked by some periods of intensive activity. He acknowledged that getting input on the process itself would be important.

Dr. Woychik noted that the 15-month timeline is designed to ensure maximum engagement from all NIEHS staff and all key external stakeholder groups, with multiple opportunities to provide input, advice, and expertise. The current SP, mission and value statements, and ongoing strategic planning efforts will be integrated into the new document, which will include new mission and value statements as well as the new, 8-10-page SP itself. Also, there will be a new "tag line" statement unique to NIEHS.

He related the proposed timeline for the process, beginning with Dr. Birnbaum presenting the process and timelines to NIEHS personnel in an informational all-hands meeting to be conducted March 1. At the same time, an email with the same information will go out to a broad base of external stakeholders. Dr. Birnbaum will also present the information at a "Director's Event" at the Society of Toxicology meeting in early March. The first input-gathering step will be web-based, using a tool designed to solicit input cost-effectively, which will be integrated with the current NIEHS website. The appropriate Federal Register notices will be published. Initially, input will be sought at a high level, concentrating on broad ideas and themes rather than specifics, with a request for so-called "Visionary Ideas."

There will be a two-day Stakeholder Community Workshop at Research Triangle Park in July 2011, which will include 200 individuals from NIEHS and stakeholder communities. All Council members, leadership at the Institute, and other invitees determined to be key strategic thought leaders in the EHS community will be included. Individuals at all levels will be invited, as will both scientists and non-scientists. The meeting will be conducted using a modified Open Space Technology format. NIEHS staff will compile the output of the workshop and solicit further input via the website, in August and September, 2011.

In mid-October, there will be a two-day, off-site at RTP Strategic Planning Workshop, with 40-50 selected NIEHS Staff and stakeholder community representatives. The outcome of that meeting will be draft mission and vision statements, and 5-8 specified Strategic Goals emerging from all of the input and comment to that point. That

information will be posted on the web in November, using the same web-based tool for public comment. At the same time, NIEHS senior leadership will meet with staff to solicit input on implementation strategies. In December, 2011 and January and February, 2012, NIEHS senior leadership will have team meetings to develop implementation strategies. In February, 2012, Council will be updated on overall progress of the process.

In February and March, 2012, the NIEHS writing team will begin to develop a narrative text for the SP based upon the goals and strategies that will have been identified, with a final draft posted on the web for public review during April, 2012. A final narrative will then be prepared and communicated to NIEHS and Council in May, 2012, with publication of the final SP planned for June, 2012.

Dr. Schnoor asked how budgetary uncertainties were approached in a strategic planning process. Dr. Birnbaum replied that they did not have an impact on strategic goals and plans themselves, but rather on implementation of the goals and plans.

Dr. LeMasters asked about the role of program evaluation, taking into account the success of past intramural and extramural programs when formulating the new SP. Dr. Woychik noted that part of the process was to look at the existing SP, evaluate its success, and assess whether there were unfinished elements that should be incorporated into the new SP. Dr. Birnbaum added the various advisory committees and councils provide oversight over all NIEHS/NTP programs, routinely and continuously reviewing all Institute activities.

Dr. Gasiewicz asked how the NIH Strategic Plan might affect the NIEHS plan. Dr. Birnbaum said that NIEHS strategic planning is conducted within the context of NIH. However, she noted that NIEHS has some unique legislated responsibilities that are different from NIH as a whole, so that NIEHS needs to look more broadly in certain areas. She mentioned that NIEHS is involved in each of the five areas of emphasis identified for NIH by Dr. Collins. Dr. Collman added that with several other NIH ICs working on new SPs, Council members should be aware of opportunities for collaboration in areas where institutes' missions might overlap. Dr. Birnbaum noted that NIEHS is inherently cross-disciplinary, and that NIH is encouraging collaboration among the ICs, but that CSR is organized along disciplinary lines and peer review of cross-disciplinary proposals can run into challenges as a result.

VI. Report of the Director, DERT

Dr. Collman briefed Council on recent activities of the Division of Extramural Research and Training.

She recapped action items that had been identified from the September 2010 NAEHSC meeting, and their resolutions.

- R01s awarded compared to other ICs: Data to be presented in budget report
- Name of transcriptional regulation program: Working on PA, name yet to be determined
- Report of epigenetics program: Scheduled for May 2011 meeting
- Council of Councils rep: Dr. LeMasters will be the new NIEHS rep
- Definition of Translational Research for P30s: Definition in RFA

Dr. Collman related several staff changes within DERT, including new hires, promotions and departures.

She presented the Biennial Report on Population Tracking for Gender and Minorities for Council's approval, which includes data from 2009 and 2010. Bars-to-Funding data were presented, along with resolutions. Approval of the report was moved and seconded, and the vote was unanimous for approval.

Dr. Collman reported on Council-Delegated Authorities, procedures delegated by Council to NIEHS staff to carry out. It was requested that Council approve a change in the authority to authorize supplemental direct costs to a Center. In the past this has applied to P30 Core Centers only; the request is to expand the delegation to apply to all Center programs, to "provide more timely response to program needs and additional flexibility." Other requested changes include removal of language specifically tied to Recovery Act policies and procedures. Dr. Lloyd asked if that meant that the language would revert to how it had existed prior to the Recovery Act. Dr. Collman replied that it would. It was moved and seconded to accept the FY 2011/2012 Council Delegated Authorities, and Council voted unanimously in favor of the motion.

Dr. Collman related a budget report for 2010 DERT expenditures. Research Project Grants (RPGs) comprised 77% of the budget, or more than $257 million. Other major items included training (5%, >$18 million), other research (3%, >$9 million), Centers (11%, >$37 million), and SBIR/STTR grants (4%, >$12 million). By activity, R01 grants were the majority, at 68%. For the Superfund, RPGs comprised 61% of expenditures, with 58% being P42 grants.

In response to the question about R01 awards compared with other ICs, Dr. Collman presented data showing the results of an analysis by Jerry Phelps. The first chart showed that the number of R01 applications had been fairly stable over the six years analyzed. In terms of the awards, the data showed that NIEHS had made a concerted effort to increase R01s since 2008, and today the Institute is the only one to show an increase in R01 funding compared to the six-year mean.

In competing awards for 2010, NIEHS made 161 RPG awards for a total of more than $50 million. Including all of the categories, the total of competing awards was 308, at more than $90 million.

Dr. Collman reported on 2010 pay lines and success rates. Overall, the success rate was 25.1%. She also described the result of a simulation analysis of what the pay lines and success rate would have been without initiatives—32%. Looking at overall RPG success rates over the past 13 years, NIEHS is well above the current NIH average, with a "big jump" in 2010 versus 2009. In terms of overall success rates for all mechanisms, NIEHS is now in the top third of NIH ICs. The R01 success rate has also been brought up substantially. She described the factors influencing success rates. In 2010, they included an increase in competing awards and FOAs, along with other factors that led to the success rate of 25%. In 2011, it is predicted that there will be fewer competing awards with a lower budget, just a small increase in FOAs, a large increase in applications, a slightly lower set-aside, and the possibility of a full year operating on a continuing resolution. Thus, the predicted success rate is just 14.8%.

She reviewed the funding opportunities that had been approved for FY 2011, and presented budget scenarios for FY 2011 and beyond. They included a larger number of applications, with predicted numbers of 113 unsolicited and 41 solicited awards. Dr. Collman mentioned that input is needed on how best to select the appropriate number of and funding for FOAs in the future. She said that new FOAs are being developed that utilize funds from other budget categories, including possible redirection of funds from Centers to RPGs, from RPGs to Centers, or from RPGs to other research. This all emphasizes the need to plan more than one year in advance in terms of budgets.

Dr. Collman presented the Division's funding philosophies and challenges.

Philosophies included:

- High scientific quality
- Maximize our support of new and early stage investigators
- Focus on awarding R01s
- Need R21/R03 program (but what size?)
- Special look at A1s and Type 2s
- Sustaining NIEHS investments
- Iterative process to balance all needs
- Try to make the most awards with the funds available

Challenges were:

- Support the breadth of EHS and also invest in emerging areas
- No targeted programs for New/ESI – ONES program is coming to an end

- Accepting large R01 grant applications – over $500K, over $750K, over $1M
- Supporting team science
- Balance unsolicited and solicited awards
- Aligning funding decisions with strategic planning

To stimulate discussion and input from Council, Dr. Collman also presented current practices and questions for the future of funding decisions.

Current practices:

- Do not have preset pay line
- Iterative process to choose grants to pay and identify those to hold
- Hold secondary assignments unless they are unprecedented scientific opportunity
- Set cuts for all awards, done in part to optimize the number of awards that can be made

Questions for the future, based upon those current practices, included whether we should do the following:

- Set a conservative pay line and advertise the pay line
- Concentrate on gray zone for strategic decisions
- Use Program Announcements to identify priority areas and implement select pay procedures
- Bring more Low Program Priority and High Program Priority applications for discussion
- Balance between R01 and P01
- Fund fewer or no large grants
- Pay fewer grants fully, but pay them – smaller or no cuts

To seed Council's discussion, Dr. Collman returned to the slide depicting the funding philosophies and challenges. Dr. Liekauf praised Dr. Collman for her presentation, stating that it allows Council to advise on the tough choices facing DERT. He asked why grants were shrinking from $68 million in FY 2010 to an anticipated $55 million for FY 2011. Dr. Collman replied that after allowing for non-competing obligations, the pool of money available for competing grants was in fact smaller. Dr. Liekauf suggested that 10% of the overall money coming into NIEHS each year be designated for the unsolicited R01 program, to ensure the R01 success rate is comparable to the prior year's rate.

Dr. Birnbaum commented that Dr. Collman's analysis of the cut-off lines without FOAs was very interesting. Dr. Collman said that the Division is acquiring a tool that will allow it to run scenarios showing the impacts of changing numbers and percentages.

Dr. Brody asked Dr. Collman to clarify her statement about the relationship between the PEPH and the R01s. She replied that the PEPH, with its various programs, has the potential to be in many different budget categories, so different mechanisms are used based on specific needs.

Dr. Lee asked if Dr. Collman had looked back at the past ten years to analyze whether funded investigators were continuing to be funded by NIEHS, or had migrated to other sources of funding. Dr. Collman said that some such analyses had been conducted, and that in some cases investigators had moved to other funding sources as a result of changes in their scientific pursuits.

Dr. McKone asked about the need to ensure continuing investment in the pipeline flow of newer and younger investigators, given dwindling budgets. Dr. Birnbaum replied that that was one of the disappointments of the inability to continue the ONES program. NIH, she said, has directed that special attention be paid to new and young investigators, to the point that given equal review scores, the early stage investigators would be preferred. Dr. Collman said that one way to protect the flow of young investigators might be to limit the number of grants an individual laboratory can receive, as is done at some NIH ICs already. She said that would tough, however, in balancing the need to consider the Institute's strategic priorities as well.

Dr. LeMasters commented in support of the idea of limiting the number of grants an investigator could get, noting that it would encourage senior investigators to pass off to younger investigators. She said it would also keep younger investigators from becoming discouraged, and would help keep them in the field. Dr. Birnbaum reiterated that NIH has mandated that there be no individual set-aside programs for new investigators anymore, although they continue to encourage significant funding levels for new investigators.

Dr. Liekauf suggested reducing awards in the future by a specific percentage, and that that would energize the research community to support future NIEHS funding. He noted that it would also empower the investigators to carry out similar cuts in their own institutions. It would also allow everyone to equally share the burden of cuts. In terms of the large grants, he felt that some should be pushed toward the P01 mechanism, if it is revived, instead of being inflated R01s. He supported a limit on the size of R01s.

Dr. Gasiewicz agreed that it would be important to find a way to continue to support and mentor young investigators.

Dr. Ramos said he had been pleased to see Dr. Collman's slide articulating some of the philosophies underlying DERT decision-making, and recommended that she continue to build upon it. He was surprised that there did not seem to be a set of guidelines for a good portfolio, and recommended that DERT formalize the brainstorming and decision-making process. He agreed with Dr. Liekauf's comments regarding R01s, but cautioned that there would still need to be some flexibility in the process to accommodate changes in the budgetary situation. He also agreed that a cap should be set on large R01s. Dr. Collman responded that it was a complex situation, and that it should be judged according to scientific priorities, rather than necessarily addressed all large R01s collectively.

Dr. Finnell recommended capping R01s at $500,000 as long as the NIEHS budget is flat or diminishing, citing "tough times and tough choices."

Dr. Lloyd asked about P01 funding, noting that the FY2010 P01s, and how the funds freed up by the phasing out of the current P01s would be distributed in the future. Dr. Collman pointed out that a thorough discussion of P01s was scheduled for later in the meeting.

Dr. Baylin expressed concern that a cut in R01s could hinder individual creativity, from which the best scientific ideas emerge. He said that perhaps creativity could be encouraged through grants involving collaborations. He hoped that the current high level of pay lines could be sustained in the future. Dr. Collman cited the VICTER program as one that exemplified Dr. Baylin's idea about smaller collaborations leading to larger initiatives.

Dr. Winn described some of the methods used at NCI to accommodate large grants, including data sharing requirements and asking for statements regarding cost savings and cost sharing.

Dr. LeMasters expressed concern that the GuLF study might pull budgetary resources from NIEHS that had not been planned for, creating a problem for the Institute. Dr. Birnbaum said that NIEHS had committed to run the program for five years. She described the funding sources in place for the initial phases of the study, including money from NIH and BP. She said it was to be hoped that BP would make another gift to cover expenses in the out years, but there is no guarantee of that. The institutes involved in the consortium project have committed to contribute money for each of the first five years. Dr. LeMasters asked whether NIEHS would be left "holding a big bag" in terms of budget for the study, even in the face of unanticipated reductions in its budget. Dr. Birnbaum said there would be opportunities to re-examine certain aspects of the budget. For example, if automatic cuts were instituted, it would affect the GuLF study as well. On the other hand, she said, NIEHS does bear responsibility to respond to an

emergency situation, and that establishment of an emergency research response capability is currently being explored, including establishing a standing HHS IRB and an ability to quickly collect biospecimens in an emergency situation.

Dr. Liekauf commented on translational research, pointing out that it carries huge costs that should be taken into account when translation is being considered, and that it could take funding away from other opportunities. Dr. Birnbaum speculated that Dr. Liekauf was defining translational research as translational medicine, and that the NIEHS definition is much broader, incorporating translation to public health as well, which is part of the Institute's mandate. Dr. Liekauf said he understood that, but emphasized that translational research requires validation, which is very expensive, with very large control groups required to see very small effects. Thus, he cautioned the Institute to be careful about requiring translation "all over the place" without sufficient funds. Dr. Birnbaum asked Council members to consider his point for the upcoming discussion about the strategic planning process.

Dr. Lee asked whether translational programs might be incorporated into the proposed new NIH center. Dr. Birnbaum replied that it was a good question, in that NIH has not actively embraced the concept of prevention. She said the new center would probably not start many new programs, except to enhance drug development.

VII. Council Discussion

Following the lunch break, Council resumed its discussion, concentrating on the strategic planning process.

Dr. Birnbaum framed the discussion by stating, "I do believe that we are about prevention. I do believe that we are the part of NIH that has a real public health mission. I do believe in one NIEHS, which means that I think it's important for the different parts of the Institute to dialog and work together when appropriate to achieve our mission. I do believe that there are areas of environmental health that we should be really moving forward in. I do believe that we need discussion about what we mean by 'the environment'…I do believe that in times of tight budget, we still have to do absolutely the best science, but maybe we can't do everything, and that it's going to be important for us to think about what we can do, what we should do, and maybe what other people can and should do as well."

Dr. Woychik acknowledged Dr. Birnbaum's remarks, and emphasized that the SP process would involve tough trade-offs, and careful establishment of priorities.

Dr. Liekauf noted the need for an integrative approach to the SP, including a scientific basis for making an investment in preventive medicine, with validation of interventions and adoption into public health practice. He urged that a certain portion of the NIEHS portfolio be investigator-driven and independent, and that time frames be realistic. He hoped that the Institute would continue to be grounded in science, with that concept at the forefront of the decision-making process.

Dr. McKone discussed the ongoing challenge of defining what the environment is. He said there are various levels of integration, for example, the blood being the environment for tissues and cells, while with ionizing radiation, the whole cosmos would be the environment. He said that failure to appreciate the various scales is one of the mistakes made in EHS research, and that it is important to pick the right level of integration.

Ms. Witherspoon agreed with the previous comments indicating that the science must be retained as the core consideration. She praised the Centers approach as being innovative, and speculated that since they continue to be funded, the results must be positive. She hoped that approach would be maintained. She also acknowledged the Institute's leadership in professional development and training.

Dr. Ramos recommended that during the SP workshops less time should be spent on the "30,000 feet view" of the Institute's mission, as that would likely result in ratification of information that's already known, and that the process could "fall through the cracks." He stressed that the most important aspect will be the implementation phase. He recommended cutting back on the vision discussion, collecting that information prior to the physical meeting, and then using that time to concentrate on prioritization, which is likely to be the toughest challenge. He recommended making the goal of the meeting identifying tangible products that would be the metrics for success at the end of the five-year period, as opposed to "esoteric brainstorming." He said that the SP should identify some thematic areas where the bulk of the strategic investment would be made, even beyond core areas. He urged that NIEHS take "ownership" of some specific thematic areas, citing epigenetics as an example, and stated that this would be a way for the Institute to make a real difference over the course of the five years.

Dr. Schnoor asked that the SP include clear recognition and expression of the fact that prevention and public health are one of the focuses of the Institute. He said that public health is inherently translational, not in the "bench-to-bedside" sense, but that people would not be in the beds in the first place. He agreed that a certain portion of the portfolio should be investigator-initiated. He also agreed with Dr. Ramos's remarks about concentrating on thematic areas where NIEHS science could really make a difference.

Dr. Carpenter agreed that prevention should be a central theme for EHS. Dr. Brody expressed her excitement to hear the director of NIEHS talk about translation as translation to public health. She said that would necessitate new standards of evidence and vehicles for translation to public health. She cited the removal of lead from gasoline as a good example.

Dr. Finnell pointed to the recent publication of results regarding *in utero* surgery for spina bifida, claiming that the surgery is now the "standard of care" for the condition, noting that of course prevention of the birth defect should be considered the standard of care. He cited that example as further reinforcement of the importance of prevention to the NIEHS mission. Dr. Birnbaum reminded Dr. Finnell that NIEHS supports 14 Children's Environmental Health Centers, several of which focus on reproductive and developmental effects. She said she sees research on developmental origins of disease as one of the Institute's key missions.

Dr. Taylor encouraged more partnerships with other institutes, as a way to amplify the available funds. Dr. Baylin agreed with the need to prioritize in specific given areas, and the concept of taking ownership of those areas.

Dr. Bradfield mentioned the need to define and explore the transcriptome, as a way to establish a baseline to better understand the impact of exposures at the RNA level. Dr. Birnbaum supported that concept.

Dr. Lee cited the obesity epidemic and the emphasis on prevention it had spawned as a good example of focus shifting toward prevention.

Ms. Hricko said that it would be important to include consideration of environmental health policy issues in the SP process, as a way to translate science into public health.

Dr. LeMasters urged inclusion of education, particularly to encourage pediatric environmental health as a subspecialty within the medical curriculum. Dr. Lee added that in her experience people interested in pediatric environmental health would combine their pediatric subspecialty degree with a Masters in Public Health degree to enter the field. Dr. Birnbaum mentioned that NIEHS is getting its first MPH oncologist coming in on rotation. Ms. Hricko added that in terms of the SP, this discussion emphasized the need for effective communication with professional associations.

Dr. Liekauf agreed with earlier remarks about the importance of emphasizing training in the SP. He also stressed the need to move environmental health into clinical practice and bring physicians into the field, investing in young physicians and making environmental health practices general clinical practices.

Dr. Lloyd noted that much of the discussion had come at the intersections of disciplines, and that much of the material in the SP would probably by definition require multi-disciplinary teams. He said that this approach would encourage visionary ideas, and should be supported financially. He wondered what the role of oceans research would be going forward. Dr. Birnbaum said that the oceans research program would be maintained. Dr. Collman mentioned that NIEHS has been working with NSF on that program, and that an RFA would be coming out.

Dr. Birnbaum reiterated that NIEHS does have some unique characteristics, including Superfund and NTP, which need to be subtracted from any potential formulation regarding a percentage of funds going to R01s. Dr. Liekauf averred that the basic sciences are at the heart of all of the funding mechanisms, which helps the Institute make logical decisions and prioritize. Dr. Birnbaum replied that no one was questioning the role of basic sciences.

Dr. Woychik said that he was overwhelmed with the input received during the discussion, which would be a basis for beginning to develop some specific ideas for the SP process going forward.

VIII. Concept Discussion: Role of Environmental Exposures in the Development of Obesity, Type 2 Diabetes, and Metabolic Syndrome

Dr. Jerry Heindel presented to Council the background and hypothesis underlying the concept. He established the fact that there has been a huge increase in obesity in the US and around the world, in both adults and children, and that it constitutes “a huge public health problem.” He related the obesity epidemic to the major research program at NIEHS, “Developmental Origins of Disease,” which explores the concept that developmental exposures lead to disease throughout life, often long after the exposure has taken place. Disease areas that have been shown in animal models to be stimulated by developmental exposures include reproductive/endocrine, immune/autoimmune, pulmonocardiovascular, and brain and nervous system disorders. The reproductive/endocrine conditions include diabetes, metabolic syndrome, and obesity. Part of the paradigm is the hypothesis that obesity could be due to disruption of the endocrine system from exposure to endocrine-disrupting chemicals (EDCs), which include dozens of herbicides, fungicides, metals, insecticides, and industrial chemicals.

Dr. Heindel said that the emerging “obesogen” hypothesis posits that “the obesity and diabetes epidemic is due, in part, to environmental exposures during development,” by controlling adipose tissue development and controlling food intake and metabolism, thereby altering the programming of the obesity and diabetes “setpoint” or sensitivity for

developing obesity later in life. An obesogen is defined as a chemical that can alter any of the affected systems. The hypothesis states that while food intake and metabolism are important, the sensitivity of the system is programmed during development, and that EDCs can alter that programming. The hypothesis changes the focus from genetics to exposure to environmental chemicals during development, which have effects that last a lifetime. This also changes the focus from intervention to prevention. Although the importance of food intake and exercise is recognized, environmental chemicals can alter the setpoint for gaining weight, affecting how much food it takes to put on weight, and how much exercise is needed to reduce weight.

As an example, Dr. Heindel shared data from a study by Retha Newbold and colleagues at NIEHS that showed that exposing mice to the strong EDC DES in early development led to pronounced obesity later in the animals' lives. He also depicted a list of chemicals suspected to be obesogens, speculating that they may represent just "the tip of the iceberg." Along with affecting weight gain, he said, researchers are also seeing altered glucose tolerance and insulin sensitivity, and increased lipids, blood pressure and cardiovascular disease, with overlaps among the various chemicals involved.

Since the early 2000s and Dr. Newbold's work, NIEHS has been working to stimulate this field. Dr. Heindel depicted a series of activities between 2004 and 2011 to that end, including various talks, publications, a listserv, and a section on environmental obesogens in the White House Obesity report, culminating in the January 2011 NTP conference, "Role of Environmental Chemicals in the Development of Diabetes and Obesity."

To describe that workshop in more detail, Dr. Heindel ceded the podium to NTP Associate Director Dr. John Bucher.

IX. Obesity Meeting Update

Dr. Bucher said that the workshop had actually lived up to, or perhaps exceeded expectations. It was chaired by Dr. Michael Gallo of the University of Medicine and Dentistry of New Jersey, and was organized by Dr. Christina Thayer of the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR). The overall goals of the workshop were:

- To evaluate the science associating exposure to certain chemicals or chemical classes with development of diabetes or obesity in humans
- To provide input to NTP and NIEHS for development of a research agenda
- To bring together diverse expertise, including toxicologists, epidemiologists, bio-informaticists, and experts in the pathobiology of disease

Workshop participants were asked to evaluate existing findings, identify the most useful and relevant experimental endpoints, identify data gaps, and consider targets and pathways for assays for inclusion in the Tox21 high-throughput screening initiative.

An NTP Monograph to be published in summer 2011 will be the product of the workshop. The workshop separated into several breakout groups that addressed charge questions provided with background documents. Dr. Bucher detailed the various breakout groups for Council, and provided a brief overview of the Tox21 initiative.

In arriving at the background information provided for persistent organic pollutants (POPs), the literature was so extensive that it proved difficult to arrive at patterns of outcomes to be communicated to the breakout group and to be included in the ultimate workshop publication. Therefore, a software and database tool called a Forest Plot Generator was developed to graphically display studies' summary results, graphically depicting associations. The tool was used in real time in the breakout groups. Dr. Bucher provided some examples to illustrate the technique.

Although all of the material has not yet been collated, some points of general agreement did emerge from the workshop:

- Maternal smoking during pregnancy is associated with lower birth weight and later excess weight gains in children (providing support for the plausibility of the "obesogen" hypothesis)
- Evidence linking high arsenic exposure (>150 ppb) with diabetes in humans is "limited-to-sufficient"
- Evidence is "sufficient" for an association between diabetes and pesticides/POPs exposures based on collected analyses of cross-sectional, prospective/retrospective, and occupational exposure studies
- Human studies are "insufficient" (in the case of phthalates) or non-existent (organotins) for evaluating an association with diabetes or obesity

Dr. Bucher also depicted a tool called Tox Pie, which is used to analyze high-throughput screening data output. He showed an example for Insulin Sensitivity, which incorporated data on more than 300 ToxCast chemical results, allowing researchers to identify specific chemicals of interest for further research. Illustrating the input received from experts at the workshop, Dr. Bucher shared a graphical representation of an insulin signaling pathway from a Harvard endocrinologist, which showed that many of the gene or pathway targets had already been included in Tox21 assays. Those that were not were identified as new gene targets for Tox21 research.

In conclusion, Dr. Bucher noted that there had been general support at the workshop for:

- Plausibility of the obesogen hypothesis
- Linkage of type 2 diabetes to certain chemical exposures
- Common mechanistic basis for certain chemical classes
- Utilization of Tox21 approaches to identify substances of potential interest
- Refinement of endpoints examined using high throughput screening (HTS) approaches

Dr. Baylin commented that the workshop was an interesting exercise for NIEHS, but wondered how it would proceed, looking at all of the information and assessing where an impact could be made. Dr. Birnbaum said that was a perfect example of an appropriate question to be addressed in formulating the strategic plan.

Dr. Gasiewicz inquired about the range of doses that had been used in the studies examined, and whether they were environmentally relevant. Dr. Bucher replied that there was a wide range, given the large number of studies. He said the HTS studies were dose-respondent, and often run at very low levels.

Dr. Lloyd wondered whether the role of the microbiome had been included, and whether the general category of oxidative stress had been examined, in terms of its central role in obesity. Dr. Bucher replied that although the microbiome is clearly a dominant factor, drawing the many chemical studies together should control the influence of the microbiome and elucidate the influence of the individual chemicals. Dr. Lloyd asked if there were data directly addressing whether the chemicals being listed are modulating the microbiome. Dr. Birnbaum said that such data does not yet exist, and that the role of any of the chemicals in question *vis-à-vis* the microbiome had not yet been looked at. Responding to Dr. Lloyd's question regarding oxidative stress, Dr. Bucher noted that it is one of the two areas being focused upon in the Tox21 program, along with nuclear receptors.

X. Concept Discussion: Role of Environmental Exposures in the Development of Obesity, Type 2 Diabetes, and Metabolic Syndrome (continued)

Praising the workshop, Dr. Heindel called it "a watershed meeting." To begin to consider what could be done with the outcomes of the meeting, he said that the field of obesity, diabetes and metabolic syndrome research fits multiple programs at NIEHS, such as the programs in disease-focused research, developmental basis of disease, endocrine disruptors research, epigenetics research, and translational research. With

that in mind, this concept is designed to be multi-faceted, incorporating investigator-initiated research, translational research such as the ViCTER Program, and initiatives involving an RFA (one-time announcement), a PAR (active for three years), SBIR grants, and NTP HTS work. He said that all of those vehicles would be used at some point, but initially the focus would be on the PAR, the SBIR set-asides, and the NTP screening. He said that the thinking is that a Program Announcement might be the best way to stimulate the field, and that although there was no specific money associated with it, the three-year window would show NIEHS's commitment and serious interest.

So, the proposal is for a PA on the Role of Environmental Chemical Exposures in the Development of Obesity, Diabetes and Metabolic Syndrome. It would incorporate both R01 and R21 mechanisms, with the multiple mechanisms and multiple years designed to stimulate the developing area. The goals of the program would be:

- To show which environmental chemicals can program increased susceptibility to obesity/diabetes, metabolic syndrome and to define the site(s) and mechanism(s) of action
- To develop biomarkers of exposures and susceptibility that lead to these diseases/dysfunctions that can be used in intervention studies
- To reduce the incidence of these diseases/dysfunctions (disease prevention) by reducing exposures

The R21 component of the program would be mainly 2-year pilot studies, designed to identify new environmental chemicals involved in these mechanisms, to delineate which chemicals cause only specific diseases among the class, to develop biomarkers of exposure and to develop and test high-throughput screens specific to these questions.

The R01 program would focus on:

- Understanding the site(s) and mechanism(s) involved in these processes
- Development and utilization of high-throughput screens to detect chemicals involved in the processes
- Understanding the interaction of genetic background, nutrition, stress, drugs, infections and other alterations (circadian, immune, and microbiome, for instance) with environmental exposures during development that could lead to these diseases/dysfunctions later in life
- Development of biomarkers of exposure and pre-disease indicating increased susceptibility

The R01 program will encourage multi-PI applications, particularly combinations of toxicologists and scientists with biological or endocrine expertise, and applications that focus on dose responses, internal levels of the environmental chemicals, and assessment of sex differences. Weight gain or glucose intolerance will not be sufficient endpoints. Dr. Heindel said that the Center for Scientific Review would set up a special Study Section to review applications under the PA.

Dr. Finnell was the first Council reviewer of the concept. He noted that it provides emphasis and focus to research on obesity, which as Dr. Heindel had pointed out, touches several different areas of interest at NIEHS. He approved of the choice of PA without a direct set-aside, given current budget limitations, showing the community that the Institute is committed without having to make cuts in other areas. He said that there were many interesting possibilities for tie-ins, such as with the knockout mouse model program. He said he had a few other minor concerns, but was generally very supportive of the concept.

The second Council reviewer, Dr. Brody, echoed Dr. Finnell's support of the concept, noting that it addresses what is clearly an important public health problem, with a substantial body of evidence supporting that this is an important hypothesis to pursue. She approved of the choice of a 3-year PAR, and the HTS assays. She recommended giving some thought to environmental measurements as well as biological measurements to help identify the major sources of exposure, which would be helpful in effectively targeting interventions.

Ms. Hricko recommended including consideration of the interaction between air pollution and diabetes in future workshops on this topic. Dr. Heindel noted that in his list of obesogens, air pollution was included.

Dr. Gasiewicz complimented the combination of biologists and toxicologists planned for the program.

Dr. LeMasters found the data presented interesting, and saw the forest plot approach as a form of meta-analysis. She was concerned, however, that when she thinks about diabetes, metabolic syndrome and obesity, environmental exposures are not the first consideration she would have when examining such effects on humans. She felt that inflammation was a more likely major pathway, the "intermediate where the action is." Dr. Heindel replied that NIEHS is very interested in inflammation as the center of many diseases, but that here the goal is to characterize a phenotype and improve human health; inflammation would be one of the pathways to be examined within that wider context. Dr. Birnbaum said this proposal would exemplify the need to focus on health outcomes that are increasing or operating at very high levels within the population.

Dr. Lloyd wondered about the practical aspects of developing and implementing new HTS methods, in terms of the long time it can take to get validation and approval. Dr. Heindel replied that it would in large part rely on the expertise and resources of individual investigators. Dr. Lloyd suggested that the program might screen the LOPAC chemical library, as sufficient to see how some of those compounds might modulate fat cell development. Dr. Heindel said that was an interesting idea, and someone could propose it. Dr. Collman added that the PA was intended to be "a big net," to stimulate ideas.

Dr. Carpenter asked about the funding success rate for PARs, and what the motivation would be to take the time to write a grant under it, if there's no funding readily available. Dr. Collman replied that this was a question that had been asked in the past for PAs, and that previously NIEHS had joined in PAs issued by multiple NIH institutes, as a way to indicate interest. She said that now the Institute is looking at the PA mechanism as one way to "stake a claim" in an emerging field, and that when funding is considered strategically, those high priority areas would be looked at closely.

Dr. Collman requested and received a motion and second to approve the concept. All Council members voted to approve, except Dr. LeMasters, who opposed the motion. The motion carried.

XI. Concept Discussion: RFA: Environmental Influences on Stem Cells in Development, Health, and Disease

Dr. Collman began the day's proceedings with a brief introduction, in which she emphasized that the concept clearances to be presented were not intended for immediate funding, but were being rolled out for long-term planning purposes. She said that NIEHS wanted Council's feedback, comments, and constructive criticism of the ideas.

Dr. Les Reinlib briefed Council on the stem cell program concept proposal. He said that improved understanding of environmental influences on stem and self-renewing cells would likely lead to:

- Insights into early events in disease pathogenesis and elucidation of their mechanisms
- Novel biomarkers, screening, and early detection
- Tools for research
- Development of ways to regulate or engineer stem cells, leading to improved therapies and public health messages for individuals at risk

This idea stemmed in part from the International Conference on Fetal Programming and Developmental Toxicity, in 2007, which concluded that fetal and early postnatal development constitutes the most vulnerable time of human life to adverse environmental hazards, and that even subtle effects can lead to functional deficits and increased risks of disease later in life, with the central nervous system, endocrine system, the immune system, and the cardiovascular system the most vulnerable organ systems.

Stem cell research in the context of environmental health would occur at an early point in the exposure-response continuum. Dr. Reinlib made the point that although this has been a subject of interest in the research community, there has not been an organized effort to focus research on the interface between stem cells and environmental exposures, with just a small, scattered list of publications over the past five years, "and we would like to jump-start that," he said.

In 2010, NIEHS convened a workshop on the Impact of Environmental Factors on Stem Cells in Health and Disease, which provided research recommendations:

- Focus on stem cells to clarify timing and mechanisms of windows of susceptibility
- Determine characteristics of stem and self-renewing cells at specific points in human development and determine effects of exposures on processes
- Produce 3D model systems that reflect physiology, especially those cells "not available," such as brain or lung cells. Long-term study of age/exposure should be a priority, and could lead to valuable panels of cells representing population diversity.

Dr. Reinlib reported that the proposed RFA would concentrate on the first two of the workshop's recommendations. He noted that several NIEHS programs and goals could benefit from stem cell research, including *in utero* exposures leading to adult diseases, early exposure and breast cancer risk, epigenetics, endocrine disruptor research, and DNA repair dysfunction and disease. The overall objective of the RFA would be "to support novel research directions leading to understanding of how environmental exposures affect lineage, function, proliferation, and survival of stem cells and self-renewing cells and to determine how this may predispose to disease." It would specifically support studies to gain insights into the role of stem cells on the nature and mechanisms of windows of susceptibility. It would be limited to the endocrine, reproductive, immune/hematopoietic and central nervous systems. It would exclude research on stem cells or lines as tools for toxicological screening, and would encourage use of NIH-approved hESC lines.

The RFA would run for five years, comprising 6-7 R01 grants, with a proposed budget of $2.5 million per year.

Dr. Gasiewicz was the first primary reviewer. He said he was “very much in favor” of the initiative, and agreed with the limited scope of the program given the limited funding available, although, he said, it may still be too expansive. He recommended focusing on the stem cell “niche” in the microenvironment, in that some exposures may be targeting the microenvironment rather than stem cells specifically. He said that *in vitro* systems should be clearly matched with an *in vivo* correlate. He mentioned that the group may also want to consider R21 grants.

Second reviewer Dr. Lloyd largely agreed with Dr. Gasiewicz’s comments.

Dr. Reinlib asked Dr. Baylin to comment also. Dr. Baylin said that it is a critically important area, but a tough area. He noted that involvement of personnel with the appropriate expertise would be vital, as the definition and characterizations of stem cells is still much in debate in certain areas. He said that collaborations would be important, in order to take advantage of research that is already going on, particularly in the area of epigenetics. Dr. Reinlib agreed.

Dr. LeMasters wondered why there had been no mention of male reproduction, with male sperm cell counts clearly declining, with potentially huge environmental influences on the fetus and developing child. Dr. Reinlib replied that although he had highlighted female reproductive issues, male reproduction was certainly not excluded.

Dr. Liekauf asked why the research was being limited to windows of susceptibility, when clearly stem cells are always present. Dr. Reinlib replied that the program is not limited to windows of susceptibility, but that they have been identified as a priority area within the program in that there is the possibility of answering important questions about them through this research.

Dr. Carpenter wondered whether an RFA was really necessary for stem cell research in this area, with so much existing research activity. Dr. Reinlib replied that although there is considerable ongoing stem cell research, there is actually very limited activity in this particular area, surprisingly. He said that the stem cell research community needs to expand its scope to incorporate the influence of environmental exposures.

Dr. Collman asked for a motion and second, which were forthcoming, and a vote, which was unanimous in approval of the concept.

XII. Concept Discussion: Transgenerational Inheritance in Mammals after Exposure (TIME): A DERT-NTP Collaboration

Dr. Jerry Heindel presented the concept to Council, in lieu of Dr. Lisa Chadwick, who had developed the concept but was unable to attend the meeting.

To understand transgenerational inheritance, he said, one must start with the developmental basis of disease. Early life is a particularly sensitive time for exposure, with organs forming, gene expression programs being established, and epigenetic reprogramming occurring. Also, it has been shown that changes occurring during development can permanently alter the potential of an organ. These are major areas of interest for NIEHS.

Dr. Heindel reported that there is evidence emerging in several areas supporting the idea of developmentally-induced diseases, including some epidemiological evidence in humans. The question, he said, is whether maternal exposures reach the fetus through the placenta and affect the baby throughout life—and whether those effects can also be passed on to the third generation. In a prenatal exposure, three generations are actually exposed…the mother (or in this case grandmother), the fetus, and the F2 grandchildren, who are exposed as germ cells within the F1 offspring.

Dr. Heindel noted that this research may be high risk, but could also be high pay-off, in that if the idea of transgenerational effects is true, "it's a huge public concern." He cited several examples of research in the area, including the best-characterized example in mammals, vinclozolin. One group of studies showed that vinclozolin exposure in F0 resulted in decreased spermatogenic capacity through the F4 generation, along with effects upon other endpoints. Other compounds implicated in transgenerational inheritance in mammalian models have included methoxychlor, BPA, TCDD, and BaP. He also depicted a study in humans that showed that the food supply a grandmother or grandfather had available to them at age 10-12 years determined the mortality risk of their grandchildren. Although it dealt with nutrition rather than environmental chemicals, nonetheless it showed a transgenerational inheritance effect in a human population.

Although the mechanism at work remains unknown, it is suspected to be related to epigenetics. Dr. Heindel showed a graphic representation of a possible epigenetic mechanism.

Recognizing that this was an area that needed research attention, NIEHS over the past year solicited feedback from the scientific community about what would be the best approach. Ultimately, the response showed that a comprehensive solution is needed. So this concept was conceived, the Transgenerational Inheritance in Mammals after Exposure (TIME) Consortium, as a UO1 grant program. The consortium is designed to bring together investigators with complementary expertise to:

- Investigate a variety of environmental toxicants
- Test different exposure parameters (timing, dose) to determine key variables
- Identify the range of resulting phenotypes and organ systems affected

- Investigate other factors impacting transgenerational inheritance (e.g., sex, genetic background)
- Analyze DNA methylation, histone modification, and other epigenetic or genetic features to determine the mechanism

The consortium is intended to include a Transgenerational Mouse Core to be run by NTP, taking advantage of its expertise in conducting multigenerational studies. The UO1 mechanism will fund Transgenerational Phenotyping Centers and an Epigenetics/Bioinformatics Core Center.

The program could begin with the NTP Mouse Core starting breeding with exposure to candidate chemicals prior to the funding of the phenotyping centers, perhaps starting with BPA or dioxin. Later, the Phenotyping Centers and Epigenetics Core would be funded. Or, perhaps all of the resources would be funded and begun simultaneously. The exact set-up is still under consideration. The concept also offers an opportunity for interaction with transgenerational researchers, whether currently funded by NIEHS or by other NIH ICs.

Dr. Baylin was first reviewer of the concept. He said there was no question that this is a "fascinating and important area of biology." However, he said, the devil is in the details, particularly in this case how the analysis and bioinformatics center would be integrated with the phenotyping center. He recommended tackling one or two questions first, limiting the scope initially, until it was seen how the initiative would work out. He said that transcriptome analysis would need to be included. All in all, he said, it is an ambitious project, but an important one, and should make a great UO1.

Dr. Bradfield was the second reviewer. He agreed with Dr. Baylin's remarks, and added that he liked the integration with NTP. With the inclusion of the epigenetics core, he was concerned that the mechanism was presumed in advance. Dr. Heindel replied that there are two questions at work, first, to define whether transgenerational effects occur, and if so, in which tissues and associated with which chemicals, and second, to look at genetics, epigenetics, and perhaps transcriptome analysis to look for mechanisms. With regard to the phenotyping centers, he said they are looking for scientists with specific phenotyping expertise in their labs. For example, they might know how to measure immune effects, or other specific factors or disease endpoints, after NTP had conducted its studies. Dr. Bradfield wondered whether that meant the experiments would need to be run again. He was also concerned that if the wrong set of compounds was picked, there could actually be a negative effect on the field, in that transgenerational effects may not be detected, when they actually do happen with other compounds. Dr. Heindel answered that that was why they desired the proposed open-ended design, with the flexibility to measure many chemicals or classes of chemicals, and not be limited to just a few compounds.

Dr. Liekauf questioned the idea of skipping F2, in that developmental effects would not be detected. Dr. Heindel said that tissues would be saved from the F2 generation, so that further study could be conducted if transgenerational effects were seen in F3. Dr. Liekauf also wondered if real life human experiences, such as women in the 1940s smoking during pregnancy, could be incorporated as testable questions. Dr. Heindel replied that there were some data regarding smoking, and that epidemiologic questions such as those proposed by Dr. Liekauf could be added.

Dr. Finnell noted that it would be difficult to establish verifiable paternity in three human generations. He added that there are existing phenotyping cores using live animals that could be used without the need to re-invent. Dr. Lee agreed with that idea.

Dr. Woychik wondered how genetic effects and epigenetic effects would be delineated in the study. Dr. Heindel said that was a good question, and some of those endpoints would need to be included. Dr. Woychik added that there are some new technological innovations that could contribute. He also stressed the importance of having a bioinformatics core coupled with the phenotyping core. He also cautioned that age-related effects in the animals should be taken into account, and that it might constitute a great opportunity to interface with the National Institute of Aging.

Dr. Winn asked about the inclusion of themes, since there is a possibility of mismatches between phenotypes and exposures. Dr. Heindel said that was definitely a goal—acquiring enough expertise to be able to look at multiple endpoints and not be restricted to particular areas, covering as much as possible.

Dr. Lloyd asked about the logistics of sending entire animal colonies to extramural sites, and normalizing the impact on potential outcomes of the various activities at various sites. Dr. Bucher said that there is some limited experience generating animals at one facility and then transporting them to another, with reliable results. So it is, he said, feasible if done properly. Dr. Heindel added that the needs of the external participants in the consortium, in terms of animals or tissues, and when, would be carefully planned for.

Dr. Lloyd noted that NIEHS has a wealth of experience with its toxicogenomics program, and that this concept is an “exponential” increase in complexity over that, so the lessons learned from the toxicogenomics program might help, particularly in striving for reproducible, reliable results from multiple sites.

Dr. Taylor wondered whether the phenotyping needed to be handled through a contracting mechanism rather than a grant mechanism. Dr. Collman said that had been discussed, but it was felt that the grant approach would give more control and flexibility.

Dr. Baylin wondered about the time frame involved with rolling the program out. Dr. Collman said it would not be the next RFA to be worked on, and that several factors remained to be worked out, including incorporating Council's feedback. She said that the vote would simply give NIEHS the necessary approval to continue to develop the program, perhaps with a Council liaison going forward. Dr. Lloyd asked for clarification of what they would be voting on. Dr. Collman said they were asking for agreement with the scientific concept being put forward, to create an initiative or series of initiatives to address the scientific questions through a targeted solicitation in the future, with the vote being a "very high-level approval."

It was moved and seconded that the concept be approved. It was approved unanimously.

XIII. Concept Discussion: NIEHS Translational Research: Proposal for an NIEHS P01 Program

Dr. Heindel presented the concept regarding restoration of a P01 program to the arsenal of grant-making mechanisms available to NIEHS, which was conceived by an internal committee.

He said that translational research programs are mechanisms for: 1) multifaceted interdisciplinary research, 2.) coordination/integration of research across all aspects of a research area, 3.) acceleration of the application of knowledge across research areas, and 4.) enhanced interactions with other ICs. He mentioned that translational research is defined in many ways, but that NIEHS would use the following definition:

> *Translational research is defined as research that involves scientists and public health professionals from the same or multiple disciplines working interactively on a common problem to stimulate the bidirectional flow of information across the spectrum, using some combination of in vitro systems, rodent models, higher models (sheep/primate), human epidemiological or clinical research, as well as research dissemination and public health action.*

He listed the considerable number of current DERT translational research programs, and noted that funding of P01s had been put on a moratorium in 2007, due to escalating costs, lack of control over the number of grants, the fact that the grants were not focused on priority areas or were not translational, the impact of the program on R01s and R21s, and the issue that there was no time limit on the grants. He said that the current thinking is that it is time to take another look and re-open the program.

Until the moratorium, in most years 3-5 P01s were funded. They were in a wide variety of areas, and many were not disease-focused or translational in nature. In terms of costs, P01s were running approximately $20 million per year for several years, which represented approximately 20% of the R1 spanning years 2004-2008. Dr. Heindel further noted that the data had shown that P01s actually were more translational than R01s, scoring 3.3 on a 1-4 translational score, versus 1.4 for R01s. It was also seen that P01s were publishing in four times as many journals as R01s, supporting the concept that they are more translational.

Dr. Heindel said that as a result of looking at the analysis of past P01s, and the institute's interest in expanding translational research, a re-initiation of the P01 program is being proposed. It would focus on increasing translational research, coordinating and integrating NIEHS research to improve its impact on public health and policy, and providing a systematic mechanism to expand interactions with other ICs. The proposal includes a $1 million direct costs cap on grants, with a minimum of three interrelated research projects. Each grant would sunset after ten years, and should focus on an identified priority area, such as a disease, toxicant, or pathway. The envisioned integration would make the P01 the hub of the NIEHS research enterprise in a given area, as it integrates with both internal and external researchers. In terms of expanded impact, the program would:

- Expand the NIEHS translational research program, increasing the impact of the research
- Be the center of the research program in specific research areas, integrating data across the research focus and increasing its impact
- Put NIEHS on a par with other ICs that have multi-component translational research programs and clinical centers, increasing impact through easier interactions and collaborations

Dr. Heindel said there were two questions to be considered. First, will Council approve the idea of restoring P01s to the arsenal of NIEHS grant mechanisms? Second, what should the P01 program look like? He presented several potential points for Council discussion based upon those questions.

Dr. Ramos was the first reviewer. He said he was pleased to see that the limitations that brought about the 2007 moratorium on P01s had been addressed in Dr. Heindel's presentation, along with how the present proposal would overcome those past limitations. He said that he is a strong believer in P01s, and so is "definitely in favor" of the proposal. Responding to Dr. Heindel's presentation of points for discussion, Dr. Ramos advocated the $1 million cap on P01s, agreed that there should be specific requirements for P01s, with a carefully drafted RFA. He said the FOA should be specifically focused, and that there should be a limit to the number of P01s funded. He

felt that face-to-face meetings would be necessary to maximize synergy among the participants. He also said that he is in favor of sunsetting, calling it “a must.”

Dr. Gasiewicz was the second reviewer of the concept. He agreed with Dr. Ramos’s comments, particularly the need to be very specific in the proposal as to what will be expected in the program. He said the desired integration must occur, and investigators should be made very aware of that requirement, including explicit metrics for success in integration. He felt that the program should be disease-focused rather than chemical-focused. He asked Dr. Heindel whether, given the present fiscal environment, there is concern that the program could impinge on other grant programs such as R01s and R21s. Dr. Heindel said that it is a concern, and that if this program were implemented, one or more other programs would be subjected to reductions.

Dr. Lee asked for clarification of the data Dr. Heindel had presented about publications from P01s. He said that it was important to note that the data he had presented dealt with the types of journals, showing the breadth of translation.

Dr. Lloyd said he was “extraordinarily” in favor of bringing back P01s. He recommended consideration of pre-meetings with interested applicants to clarify the specific desires for the program and avoid misconceptions.
Dr. Finnell said that he too was extraordinarily supportive of the P01 concept, particularly to help balance the NIEHS research portfolio. Dr. Heindel clarified that the intention is to work in areas that may already be well-developed, but need integration to help move the field forward.

Dr. Liekauf said he was also in favor of the proposed concept, but felt that a cap of $1.5 million might be more realistic. He also supported the idea of having a theme each year, but that it might be more practical for the researchers to run parallel themes and keep them going for a few years. He also wondered what was wrong with a ten-year grant. Dr. Ramos said he did not like the idea of a ten-year grant for this mechanism, in terms of accountability and review.

Dr. Bradfield inquired about a possible argument against P01s regarding Congressional oversight. Dr. Collman said she was not aware of any specific problems related to P01s. Dr. Bradfield added that he was not comfortable with the idea of specific focus for the grants, in that creativity could be stifled. He said the door should be left open for exciting new ideas. He also argued against the idea that people need to meet face-to-face. He was concerned about the projects potentially being cost-ineffective, due to the need to charge indirect costs to external collaborators.

Dr. Gasiewicz agreed that the issue of indirect costs needed to be addressed. He said he agreed with the idea of sunsetting, but that some of the projects might be very long-

term, and that there should be a provision for renewal, perhaps with conditions for renewal that would be different from the conditions for a new proposal.

Ms. Hricko added her support to the P01s concept. She agreed with Dr. Bradfield's hesitation regarding focusing the proposal versus creativity of ideas, in that a researcher with great ideas may be unable to apply because they do not fit the theme.

Dr. Lloyd asked whether there had been an analysis of the impact of sunsetting programs. Dr. Collman replied there had never been any sunsetting, so there was no data. Dr. Lloyd asked if anyone had looked at grants entering their last or next-to-last year in terms of productivity. Dr. Collman said that other ICs did explicitly state that support for a particular program would only run for a specific number of years, but she was unaware of any analysis such as Dr. Lloyd was suggesting. He recommended that the issue be looked at. Dr. Heindel added that 70% of the prior P01s had ended before ten years, of their own volition. Dr. Lloyd said that that supported the idea that the peer review system is adequate to weed out unproductive programs.

Dr. Collman asked for and received a motion and second for approval of the concept. Council voted unanimously in favor.

XIV. Concept Discussion: Research Resources for the Environmental Health Sciences

Prior to the presentation of the concept discussion, Dr. Birnbaum briefly updated Council on a conversation she had just had with NIH Director Dr. Collins and other IC directors regarding the status of the budget. It was still unknown what the FY 2011 budget would be. The House budget, HR1, would cut NIH $1.63 billion, reverting back to 2008 budget levels. The President's budget, as she reported in her presentation, allowed a 2.4% increase in the NIH budget. She reported that part of the HR1 language called for RPGs not to exceed $400,000, and that although it was unlikely that bill would be enacted, that was the sentiment being expressed in Congress, and attention should be paid. Ultimately, she said, "it's what it is, and who knows what it is?" Dr. McKone asked about the logistics of working on a continuing resolution, and whether the new budget started once it was adopted, or whether previous funds would need to be accounted for. Dr. Birnbaum confirmed that the latter was the case; that ultimately the funding total would need to be in line with the budget.

Dr. David Balshaw of the Center for Risk and Integrated Sciences presented the concept on research resources to Council.

He said that this concept had built on some of the messages heard from the September 2010 Council meeting: the need for support of centralized access to advanced technologies, the fact that the cost of science is increasing but the resources to support it are not, and the need for support of discovery-driven science. He delineated the NIH mechanisms to support centralized resources, neither of which has ever been offered by NIEHS: R24, for Research-Related Research Projects, and P41, Biotechnology Resource Grants. Either mechanism, he said, could fit for the plans to provide centralized resources under the concept. Both have been used extensively by other institutes – in FY2010, 17 ICs offered R24s, with a total of 232 awarded, with an average direct cost of $475,000. There were 87 U24 cooperative agreements awarded at an average direct cost of $1.2 million, with a median of $840,000. Other ICs use these mechanisms to support, for example, a tissue resource center, 'omics capabilities, and databases.

Within the proposed NIEHS program, the desire is provide access to unique capacity, technology or tools to the environmental health sciences (EHS) community. A broad range of themes could be addressed, including high throughput screening (HTS) systems and chemical libraries, unique 'omics capabilities, imaging, exposure assessment technologies, underutilized animal models, and databases—unique capabilities that individual institutions would be unlikely to possess. The award would support maintenance of the resource, unrestricted access to the resource by the EHS user community, marketing/outreach activities, and a minimal level of support for continued development and refinement of the resource, expanding its capacity and capability.

Implementation would involve a multi-year PAR for R24 or P41. It would be broadly focused, with themes reviewed each year to add or decrease emphasis on particular topics. An RFI would be released to assess the community's needs. The PAR would involve a small number of awards—1-3 per year, which would be five-year, renewable awards with direct costs between $500,000 and $1 million. When appropriate, some of the awards may be converted to cooperative agreements (U24). Continuing evaluation would be a critical element of the program. There would be strict annual review of non-competitive renewals, in this case including a requirement that the resource be provided to and used by the EHS community. For long-range evaluation, there would be a survey of users to assess the benefits to their research programs, the discoveries enabled by the resources, and publications directly attributable to support from R24 resources.

Dr. Taylor was the first reviewer of the concept. He said that it hinges on institutions having high-end instrumentation with excess capacity. By depending largely on the maintenance of existing instrumentation, it will require careful oversight to be successful, with a yearly review of efficiency and productivity. He agreed that there may

be a greater need for a program such as this if the NCRR is abolished. He added that as remote operation of high-end instrumentation becomes more commonplace, it would add to utilization and also be valuable for training purposes.

Dr. Baylin was second reviewer. He echoed Dr. Taylor's comments. He felt that it was very critical to maximize the ability of individual laboratories to access "big science" technology. He said the program would need to be planned so that there is rich science and need for the use of the technology, and care would need to be taken that the data did not "evaporate" without being analyzed due to lack of other resources such as bioinformatics.

Dr. Liekauf asked if it had been thought about to partner with NTP. Dr. Balshaw replied that it had considered, and would probably be appropriate in some situations, such as HTS, chemical screening, and imaging, but not others.

Dr. Lloyd noted that there is a very limited number of sites capable of the combinatorial chemistry necessary to move lead molecules forward, and that it might be an area to be considered for this program. Dr. Balshaw replied that it was likely that the proposed new Translational Center would probably be pursuing that capability.

Dr. Woychik said that with the increasing emphasis on collaborative science and team science, programs such as this would be likely to proliferate. He wondered about transitioning resources from centers that were being terminated. Dr. Balshaw said they had not thought about that, because he would anticipate that the resources would be in place already at the various sites. Dr. Woychik also commented that it might be worth considering a charge-back system. Dr. Collman added that an idea like that could be asked about in the RFI.

Dr. Collman requested a motion and second to accept the concept, which were provided. Council voted unanimously to approve the concept.

XV. Concept Discussion: Undergraduate Training

Dr. Michael Humble presented the concept on Undergraduate Training to Council. The concept covers both ongoing programs and new programs.

One current program, an R25, is called STEER: Short-Term Experiences for Research in the Environmental Health Sciences for Undergraduates and High School Students. Eleven of the 8 to 12-week summer programs are currently funded, at a total cost of $600,000. Each program enrolls between four and eight students. Due to increased ARRA funding, enrollment expanded over the past two summers. Over three summers, the programs have supported 65 high school students, 266 undergraduates, and 2

teachers. Entering the fourth year of the five-year program, the time is right to consider the next RFA, Dr. Humble said.

As it happens, the NIH has recently created and released an omnibus program nearly identical to STEER, called the NIH Summer Research Experience Program. NIEHS is participating in the NIH program, transitioning the STEER program from a once every five years RFA program to a program funding several applications per year from the omnibus announcement. The ultimate goal, according to Dr. Humble, is to create and maintain a steady state portfolio of 12-15 programs, at an approximate cost of $60,000 per program, or a total of $900,000 for 15 programs, which would fund approximately 90 summer participants.

There are also two programs under development to accommodate diversity in undergraduate training: the Undergraduate Program (UP) to Environmental Health Sciences Research Careers (R25), and the NIEHS Limited Competition for Diversity Undergraduate Student Training Supplements. The R25 UP program would provide funding for junior and senior-level undergraduates from the diversity categories to gain hands-on experience with EHS research activities. Applicant programs would need to demonstrate both a strong STEM undergraduate program with underrepresented students interested in pursuing a career in EHS, and a strong graduate program in EHS, as evidenced by a funded NIEHS T32 training program, a strong base of funded EHS research, and/or a proposed collaboration between an undergraduate and graduate program in EHS. The program would involve:

- 2 academic years of student participation, junior and senior years
- Support for the undergraduate for up to 15 hours/week during the academic year and 40 hours/week during the summer
- $1000 funding for local travel or travel to scientific meetings
- $10,000 limited funding to offset the time commitment of administrators
- Awards to either undergraduate or graduate institutions
- A program with four students = ~$60,000 per year
- $500,000 total NIEHS investment per year, ~30 students

The other new program, the NIEHS Limited Competition for Diversity Undergraduate Student Training Supplements, would offer supplements to the NIGMS T34 MARC U-STAR undergraduate training programs—the NIGMS Minority Access to Research Careers (MARC) Undergraduate Student Training in Academic Research (U-STAR) Awards. This would provide support for undergraduates who are underrepresented in the biomedical and behavioral sciences to improve their preparation for high-caliber graduate training at the Ph.D. level. The program also supports efforts to strengthen the science course curricula, pedagogical skills of faculty, and biomedical research training at institutions with significant enrollments of students from underrepresented

groups. There are currently 55 of these T34 programs with approximately 600 participants. The purpose of the NIEHS program is to offer supplemental funding to active NIGMS T34 programs to place a pre-determined number of students into summer research experiences in EHS. It is estimated that each student so supported would cost between $20,000 and $25,000, so a total NIEHS investment of $500,000 would support 20-25 students. To help students find EHS research projects, the NIGMS has a matching program—a database including all of the programs, mentors, and students and their interests. The program matches them with T32 training program. Part of this proposal is that the NIEHS T32 training programs be entered into the database, so that students with EHS interests would be able to access the appropriate programs. Dr. Humble reported that NIGMS was very interested in this proposal.

He also updated Council about an existing program, in which NIEHS since 2007 has offered administrative supplements to NIEHS grants enabling the PIs to provide summer research experiences for high school students and undergraduates. Over the two years (2007 and 2008) of NIEHS funding, 26 summer supplements were funded at a total cost of $200,000. In 2009, ARRA funding allowed expansion, with more broadly defined eligibility. In 2009 and 2010, 117 summer supplements were funded, with 360 summer positions created, at a cost of $3.6 million. In the absence of ARRA funding, the plan now is to return the program to its original, smaller scale, with a total of 20 supplements in 2011 at a cost of $200,000.

Dr. LeMasters was the first Council reviewer. She said she strongly supported the training program. She suggested that R21s be added to the list of grants eligible to participate. She asked if seniors who had graduated would still qualify for a summer experience, which Dr. Humble confirmed. She mentioned that medical students generally have one free summer, and that finding a way to support them in an EHS research project would help develop a pipeline of physicians with increased awareness of EHS. She also suggested for the high school or undergraduate programs that an abstract or poster session at the end of the summer training sessions would be helpful.

Dr. Ramos, the other Council reviewer, also liked the concept. He clarified that as long as a grant is active, it would be eligible for the supplemental support.

Dr. Schnoor expressed support for the programs, particularly the targeting of underrepresented groups.

Ms. Hricko asked about the tuition allowance. Dr. Humble clarified that it is in fact tuition during the school year. Ms. Witherspoon expressed her strong support of the concept. She asked why the UP program was restricted to students' junior and senior years. Dr. Humble said that feedback they had received indicated that it was the best

timeframe, but that it might be possible for a student to get involved following his or her sophomore year as well.

Dr. Woychik asked if there had been any assessment of how much demand exists for programs such as these, particularly in light of STEM education today. Dr. Humble said he was not aware of any data on that.

Dr. Ramos added that metrics of success would be useful, gathering data to help future decision-making.

Dr. Collman asked for and received a motion and second to approve the concept. Council voted unanimously to approve.

XVI. Concept Discussion: GEOHealth Collaborative Hubs

Dr. Humble also presented this concept to Council. The GEOHealth Collaborative Hubs program is being developed by the Fogarty International Center (FIC).

For the past 15 years, NIEHS has been collaborating with the FIC, CDC and NIOSH in a program called International Training and Research in Environmental and Occupational Health (ITREOH). It is a capacity-building program designed to provide research training to scientists in low- and middle-income countries (LMICs). The awards are typically made to US institutions who are collaborating with institutions in the LMICs. Begun in 1995, the INTREOH program is now in its third cohort. Currently there are 16 awards totaling $2.4 million per year. NIEHS contributes approximately $600,000 per year.

Dr. Humble reported that the program is now at a point at which it is appropriate to consider what the next version should be. The key would appear to be sustainability, with the desirable characteristics to include a critical mass of first-class scientists, support and recognition by the national government, effective and transparent administrative capabilities, and the involvement of multiple international collaborations and funding streams.

With those needs in mind, the FIC has now created a next-generation program called the Global Environmental and Occupational Health Collaborative Hubs for Research and Training (GEOHealth). It would create regional hubs that link US and overseas institutions, building on ITREOH institutions, international cancer networks, infectious disease centers, WHO centers, and existing NIEHS/NIH investments. “The idea is to catalyze hubs that are bigger than just the funding coming from Fogarty and NIH,” said Dr. Humble. With those multiple collaborations, it is expected that the program would be more sustainable.

Research, training, curriculum development and policy support would continue to be the program's major activities, focusing on the core sciences, which include epidemiology, biostatistics, genetics, environmental science, toxicology, and systems science. Areas of focus would be determined by what a given hub might find to be important in its region.

There would be fewer programs under this schema, but they would have larger funding. With the collaborations involved, there would be multiple PIs. The applications would be paired, and there would be one priority score. Under GEOHealth, the awards would be split between the US and foreign institutions. FIC envisions three US institutions with complementary strengths being involved in an award, with subcontracts going to the overseas site.

Council at the FIC has cleared the concept. They hope to release the PAR in summer of 2011, and ultimately for the awards to be given out in the summer of 2012.

Dr. Phan was the first Council reviewer. He said it was "clearly a meritorious and worthwhile program." He was concerned about the "miniscule" amount of money being invested, and questioned the program's impact given minimal contributions. He said he would not recommend that the BRIC (Brazil, Russia, India, China) countries be part of the program, an issue that Dr. Humble had mentioned was still under consideration by FIC.

Dr. Schnoor agreed with Dr. Phan's comments, and said he was very supportive and favorable, based on his own experiences. He also agreed with the goals of the program, and recommended that the BRIC countries should not be funded, concentrating on the LMICs. He felt that the program should be "less US-centric" than it is now, and should focus more on the needs for research capacity-building of the host country. He said he would like to see more awards in the program.

Dr. Humble clarified that the GEOHealth program would fund one hub per region, with each hub receiving approximately $600,000, which would be much larger than the awards under ITREOH. Dr. Collman added that when FIC personnel had visited NIEHS, they had expressed a desire to increase the number of NIH institutes participating, to allow more hubs to exist, while maintaining the environmental focus. They also asked NIEHS to increase its funding commitment. Given current budget uncertainties, NIEHS asked FIC to switch their focus to create the 3-year PAR, in which each year could focus on a different area of science, or region, or need, and institutes could then vary their involvement based upon their interest. FIC, she noted, was flexible and saw those as positive components of the program.

Dr. Balbus commented that the program was a good opportunity to work with other ICs and leverage resources, as well as increasing collaboration with agencies such as USAID.

Dr. Phan said that it could be possible to tighten the focus of the program, increasing impact in the focused area, especially in light of the diminishing value of the dollar.

Dr. Collman requested a motion and second for approval of the concept, which she received. Council voted unanimously to approve the concept.

XVII. Worker Training Program and ARRA

Mr. Chip Hughes updated Council on the Worker Education and Training Program (WETP) and ARRA. He noted that it was the second anniversary of the signing of ARRA, the American Reinvestment and Recovery Act, and showed a video depicting the impact of ARRA WETP funding on communities.

Following the video, one Council member called it “awesome.” Dr. Taylor asked Mr. Hughes if the program is still ongoing. He replied that WETP is still ongoing, but the stimulus money is gone. Dr. Birnbaum said that WETP is a large part of the NIEHS Superfund program, and that the point of the video was that the stimulus funds were able to enhance the program dramatically, illustrating the utility of the stimulus funding itself.

XVIII. Division of Intramural Research (DIR) Update/Introduction

Acting DIR Director Dr. David Miller updated Council on recent division developments, and introduced the Scientific Lecture.

The search continues for a permanent Director for the division. New hires for DIR include Drs. Humphrey Hung-Chang Yao, Richard Kwok, Irene Whitt, and David Kurtz. Dr. Serena Dudek has been awarded tenure. Dr. Miller also went over the list of award winners from the 2010 Science Day, which included posters and oral presentations from trainees. He briefly described the eight top DIR papers published in 2010 – four regarding inflammation and oxidative stress, and one each on environmental epidemiology, cellular stress, gene regulation, and environmental carcinogenesis.

He introduced DIR Senior Investigator Dr. Dudek, who was presenting a scientific lecture to Council regarding her work in synaptic plasticity.

XIX. Scientific Lecture: Dr. Serena Dudek: "New Insights into Regulating Synaptic Plasticity: Implications for Autism and Schizophrenia"

Dr. Dudek told Council that the work emerging from her laboratory had only been going on for the past five years, and that she and her co-workers have been fortunate to have made a number of original discoveries concerning a much-neglected part of the brain, with important implications for autism spectrum disorders (ASDs) and schizophrenia, both of which involve abnormal social behavior.

She explained that human brain development takes place in two stages. First, there is the generation of the gross structure we can all see, which mostly takes place prior to birth. The second critical stage is the refinement of the microscopic structure, when connections are formed between neurons, known as synapses. Once they are formed, synapses can be strengthened and maintained (as in learning), or, conversely, weakened and eliminated, according to experience. She said that both processes are studied in her lab, as they play a critical role in the formation of the micro-circuitry of the brain, and rely on the animal interacting with its environment. Although learning persists into adulthood, it has been shown that there are critical periods for some of the processes that only occur during early postnatal development in some brain regions. These critical periods allow experience to actually shape brain circuitry, but also make the developing brain particularly vulnerable to environmental toxicants. She said she has been particularly interested in the regulation of these critical periods, that is, how synaptic plasticity is regulated across brain regions and stages of development. Her findings, she noted, have particular relevance to ASDs and schizophrenia, both of which strike at distinct periods of development.

To study synaptic plasticity, the researchers use electrical stimulation of excitatory synapses (from rat brain hippocampal slices), which respond robustly. By measuring electrical changes with a precisely-located electrode, plasticity can be detected and quantified. In experiments using a brief period of high-frequency stimulation, the size of the synaptic response can be increased indefinitely, a phenomenon called long-term potentiation (LTP). LTP is thought to provide the synaptic basis of learning and memory. Lower-frequency stimulation, in turn, can induce a lasting depression of the response, called long-term depression (LTD). LTP and LTD are not independent, but exist along a continuum.

Dr. Dudek showed data illustrating the experimental relationship between frequencies of stimulation and LTD or LTP responses – a frequency/response curve. It has also been shown that different frequencies lead to different postsynaptic calcium levels that result in kinase and phosphatase activity. Protein phosphatases are known to mediate long-

term depression, and protein kinases underlie LTP. Any gene mutation or environmental toxicant could modulate the likelihood of getting LTP or LTD. This is important because during development, if there is a situation enhancing LTD, leading to synapse pruning, it has the potential to lead to lifelong consequences in cognition. She noted that subtle disruptions of the microcircuitry could be related to developmental disorders such as ASDs or schizophrenia, which are noted to affect the thickness of the neocortex – thinning in the case of schizophrenia and thickening in the case of ASDs. Overlaying the graph with changes predicted for autism and schizophrenia, she showed that ASDs might involve less-than-normal pruning of synapses, while schizophrenia may involve more-than-normal thinning.

Most of the studies of synaptic plasticity have been performed in the CA1 region of the hippocampus. However, Dr. Dudek's group noted that CA2 neurons express a number of genes that also appear in areas of the brain that are not plastic. They wondered whether some of those genes might be involved in regulating plasticity, and so began a series of experiments involving neurons in the CA2 region. Neurons in CA2 are also spared in several insult models, such as toxin/toxicant exposure, hypoxia, seizure, and trauma. The researchers found that CA2 neurons were highly resistant to most protocols for inducing synaptic plasticity through LTP.

Looking deeper at why CA2 neurons are so resistant to synaptic plasticity, several factors were discovered to have an influence, including three that Dr. Dudek said she would describe in more detail—Pep-19-mediated calcium extrusion, A1 adenosine receptors, and RGS14-dependent Ras signaling.

She noted that calcium plays an important role in synaptic plasticity, particularly that coming through NMDA receptors. Also, a number of calcium-regulating proteins are expressed in the CA2. The team compared calcium regulation in CA2 and CA1 neurons. Using a fluorescence probe, the presence of calcium in response to stimulation was measured. As expected, a much smaller calcium response was evoked in the CA2 neurons than the CA1…approximately one-quarter of the CA1 calcium signal. By using different dye concentrations, the neurons' endogenous calcium buffering capacity could be detected. If it is true, she explained, that calcium alone could regulate plasticity in CA2, and then it should be possible to restore LTP to CA2 neurons by increasing calcium influx to overcome the buffer capacity. That strategy, in fact, worked, revealing that CA2 neurons have the necessary machinery in place to express LTP just like CA1 neurons, but that limited calcium levels restrict that expression. Adding a similar amount of calcium buffer to CA1 neurons and looking at the effect on LTP, actually had little effect, raising the question of what other factors

could be limiting calcium in CA2 that could block LTP.

It was found that extrusion is also important. Calcium extrusion is proportional to buffering, and so is four times higher in CA2. The team discovered that one or more proteins may be present in CA2 that modulate calcium extrusion, with Pep-19 identified as one possible protein at work in the process. They took a commercially available analog of Pep-19, camstatin, injected it into CA1 neurons, and found that it increased calcium extrusion and blocked LTP there. Adding a calcium pump inhibitor to CA2 neurons restored LTP.

With this new knowledge of synaptic plasticity, the behavioral consequences of manipulating it remained to be seen.

Dr. Dudek reported on experiments from Emory University, in which the researchers knocked out a CA2-enriched gene, characterizing RGS (regulators of G protein signaling) proteins, which are implicated in synaptic plasticity. One in particular, RGS14, is likely to be a scaffold for many signaling proteins that have been implicated in synaptic plasticity, such as Ras. In RGS14 knockout mice, learning was enhanced in the animals. They further found, however, that there was no long-term effect on potentiation in the CA1 synapses of the knockout animals. At that stage, the Emory team (Hepler lab) contacted Dr. Dudek and her group to take a closer look.

The Dudek group found that LTP is naturally suppressed by RGS14 in CA2 synapses in that when they measured the response to high-frequency stimulation in CA2 neurons from the knockout mice, they found robust LTP. They also found that inhibition of the ERK/MAPK signaling pathway blocked nascent LTP in the CA2 neurons of the knockout mice. So ultimately, it was found that knocking out RGS14, a scaffold protein in spines and dendrites of CA2 neurons both increases synaptic plasticity in CA2 and enhances learning and memory.

The next series of experiments used caffeine, which is a well-known antagonist of the A1 adenosine receptor (A1R), which is highly enriched in CA2. It was found that orally administered caffeine enhances synaptic responses in CA2. In CA1, there was no effect. Even *in vitro*, the effect in CA2 was rapid and pronounced. A1R antagonists were shown to potentiate CA2 synapses *in vitro*, changing the actual size and structure of the dendritic spines—a structural correlate of LTP.

Experiments showed that caffeine-induced potentiation does not require NMDA receptors or calcium, but does require Protein Kinase A (PKA).

For caffeine, it was shown that A1R antagonists induce potentiation in CA2 synapses, that there is a structural correlate of LTP, and which is independent of calcium but dependent upon cyclicAMP (cAMP) and PKA.

The group wondered whether CA2 neurons express synaptic potentiation at all, or if there is some way to induce it in a behaviorally relevant way. It turns out that the social neuropeptides, such as vasopressin, can do so. They also are known to modulate social behavior. They stimulate calcium signaling in neurons through G protein coupled receptors, notably the oxytocin and vasopressin receptors. It had been seen previously by researchers at NIMH that vasopressin 1b receptors are highly enriched in CA2 pyramidal neurons, and are only found in the CA2 cells in the brain. Knockout mice lacking the receptors had impaired social recognition memory, and Dudek's group found that agonists of both oxytocin and vasopressin 1b receptors induce synaptic potentiation in CA2 neurons, with a response similar to that of caffeine. Thus, the social neuropeptides may serve to integrate social cues into memory systems.

In response to Dr. Dudek's group's discovery of the stimulation of synaptic plasticity in CA2 by oxytocin, another group in DIR has engineered a cell-based screen for disruptors of oxytocin signaling through Gq. Of eight compounds tested initially, two flame retardants were found to be active as antagonists of oxytocin-mediated signaling. Tests will continue to see if the compounds impact plasticity.

Summarizing, Dr. Dudek's team has discovered that due to a large number of plasticity-preventing genes, the CA2 region of the hippocampus lacks the basic cellular mechanism underlying learning – synaptic LTP. Nevertheless, two of the social neuropeptides and caffeine can potentiate synaptic responses in CA2, despite the large number of plasticity-limiting proteins present. She noted a CA2-enriched molecule called Epac2; a GEF that has been identified as a novel cAMP target (but PKA-independent) is localized to dendritic spines and has been shown in other neurons to modulate LTD. Epac2 variants have been shown to strictly segregate with autistic family members. As they are rare, Epac2 mutations do not fully account for the association of the chromosomal region with autism, but this factor does lead to consideration that disruption of CA2 function may have profound consequences on social behavior, by altering development of an important module for social information and memory.

Schizophrenia shares with autism an inability to process social cues to form appropriate social behavior. It has been shown that there is a loss of inhibitory interneurons in CA2 that could similarly effect plasticity, or impact the circuitry in a way that would mimic Epac2 mutations. The difference would be the large difference in developmental onset, where it is possible that much of CA2 in schizophrenic patients develops normally but is later impaired. Thus, the two diseases may share a common etiology, but differ drastically in manifestation as a result of the impact of age of onset.

Dr. Bradfield asked Dr. Dudek to explain the term "strictly segregates" in reference to the autism gene she mentioned. She explained the correlation between the presence of specific variants and the presence of autism. Dr. Bradfield asked if there was any effort to understand how the allele frequencies are changing over time, in terms of the relative roles of genes and environment in autism. Dr. Dudek said that was "a hot potato" right now, but did not cite any specific research. She said one of the considerations is the increase in diagnosis of autism.

Dr. Taylor asked about the rapid increases in spine size, and whether receptor density also increases over time. Dr. Dudek confirmed that that was probably going on. Dr. Taylor said they must be "lying in wait," since the effect happens so rapidly. He asked if she would predict the same effect for the vasopressin receptors. She said she would.

Dr. Woychik asked about the mutations in the Epac2 gene associated with autism, and whether there is any evidence that there may be copy number variations in the gene also associated with the phenotype. Dr. Dudek said that she was unaware of any inquiry about that.

Dr. Dudek concluded by noting that this is a very exciting area of research that could turn out to be quite important to our understanding of these psychiatric disorders.
Ms. Hricko asked Dr. Dudek to describe her career trajectory and how she acquired her sense of scientific curiosity. Dr. Dudek replied that she had been interested in the brain since high school, and had been working on synaptic plasticity since her undergraduate years.

XX. Partnerships for Environmental Public Health: Evaluation Metrics

Dr. Christie Drew briefed Council on the draft version of the PEPH Evaluation Metrics Manual.

The Partnerships for Environmental Public Health (PEPH) is an umbrella program created by NIEHS in 2007. It is intended to prevent, reduce or eliminate environmental exposures that may lead to adverse health outcomes in communities, and to increase

the impact of environmental public health research at the local, regional, and national levels. Partners include scientists, community members, educators, health care providers, public health officials and policy makers. The PEPH "umbrella" includes many major programs conducted or supported by NIEHS, including several of the Centers programs, each of which has a required community-based component.

The program has recently been re-envisioned in response to an RFI and a workshop conducted in 2008, one of the biggest challenges for grantees in this program is measuring their success, since many of their partnering and outreach activities are not published in the scientific literature. Thus, NIEHS has undertaken to develop an evaluation metrics manual, in part to establish a common language of evaluation among those involved in PEPH projects, to make the whole process of evaluation a bit less daunting for those unaccustomed to it.

The manual is intended to be a tool for grantees to develop their own success metrics, as opposed to imposing those metrics upon them. It is designed to show grantees how laying out program activities, outputs, and desired impacts can help lead to program metrics, but it is not intended to be proscriptive. A metric is defined as a measure of magnitude (or another characteristic). All metrics are not equal, in that some are much easier to understand and apply than others. The philosophy is to employ a goal-based logic model to generate metrics.

The focus in the manual is assistance in how to lay out activities, outputs, and impacts—both process measures and outcome measures. It is laid out in the following chapters:

1. Introduction
2. Partnerships
3. Leveraging
4. Products and Dissemination
5. Education and Training
6. Capacity Building
7. Evaluation

Each thematic chapter contains an example logic model, along with more detailed entries for each of the three "boxes" in the model (activity, output, and impact), and a summary table of all metrics in the chapter.

Dr. Drew focused on the Partnerships chapter. PEPH partners foster partnerships by involving stakeholders in the research process, empowering stakeholders to reduce exposure and improve health, and having broad applicability to other research programs beyond NIEHS. The logic model example for partnerships included five activities, four outputs, and five potential impacts.

She described the Alaska Community Action on Toxics organization as an example, specifying its characteristics, core values, and interdependent strategies. She built a sample logic model based on the group's activities, outputs, and impacts.

For the first activity, identifying partners, Dr. Drew described metrics for identifying partners, providing several examples based upon a mixed methods approach incorporating both numbers and narrative approaches. For each box in the logic model, there is a similar box of suggested metrics. In the examples of output in the logic model, she focused on one delineating translation as an output, which tied to a box listing several examples of metrics of success in translation. As an example of an impact box, she focused on "sustainable partnerships," and then showed the box depicting potential metrics to measure success in that area.

She also showed the logic model for the Leveraging chapter, and provided an example of an activity, Leveraging Infrastructure. She highlighted the inclusion of elements such as existing products related to the project (e.g., presentations, newsletters, brochures, etc., existing IRB applications, previous grant applications, etc.) and organizational and administrative resources.

The chapters are available in the "Materials" section of the PEPH website, where there is a feedback form. Chapters will be revised based on comments and feedback, with a deadline of March 15. A revised draft will then be circulated.

Ms. Hricko said that she felt that the manual would be a tremendous resource, and thanked Dr. Drew for the effort. Dr. Brody agreed, and felt that it will be quite useful as a planning tool for people developing new projects. She felt that there was a need to develop forums for "describing things" versus "counting things," which can be tricky.

Dr. Schnoor predicted that the manual, when completed, would be used by people writing grant proposals, and would be valuable in this time of needing to do more with less, as evaluation tends to be an area cut in tight budget circumstances. Dr. Drew said one of the reasons for the manual was to provide assistance in laying out a clear data collection strategy at the outset of a project, "and data is what speaks, it's what speaks to Congress, it's what speaks to Council … [data provide] compelling evidence. He also stated that you have a much better chance of making your case if you had a strategy all along to collect the pieces of information that you need to roll up into that impact.

XXI. R03/R21 Grant Program Analysis

Mr. Jerry Phelps presented to Council on behalf of a larger group of NIEHS personnel who contributed to the project.

He reported that a question had come to the DERT Evaluation Planning Group regarding how much NIEHS is spending on R03s and R21s, and what is the institute getting for that investment, as in whether the investments in small grants lead to successful RPG awards. It was discovered upon investigation that between 1996 and 2008, NIEHS spent $120 million on the two mechanisms.

The mechanisms are designed to fund small grants. R03s have a maximum of two years of funding, with direct costs of up to $50,000 per year. They are not renewable, and are intended to support new, exploratory and developmental research projects by providing support during early stages of project development. R21s also have a maximum two years of funding, with direct costs not to exceed $275,000. They are also not renewable and are intended to support preliminary or developmental types of projects that are typically high risk or high impact. Mr. Phelps added that the mechanisms may now be more attractive in terms of trying to reduce the average cost of NIEHS-funded research projects.

He noted that the study group began its analyses with three working hypotheses:

1. R03 and R21 grant mechanisms lead to more complex grant (RPG) applications
2. "Subsequent" RPGs (i.e., RPGs that follow on one of the smaller grants) have a higher success rate than their comparison group
3. Subsequent RPGs produce more and higher quality publications faster than RPGs not resulting from an R03 or R21

For the purposes of its analyses, the group called R03s and R21s "parent grants," "small grants," or "F_0" grants. Subsequent grants were known as "matched offspring," "progeny," or "F_1" grants. They defined "success" as an R03 parent grant leading to a subsequent R21 or larger RPG grant (e.g., R01), and an R21 parent grant leading to a subsequent larger RPG grant. They found that:

- Between 1996 and 2008, there were 408 R03/R21 grants awarded to 386 Principal Investigators.
- There were 509 potential "offspring" candidates—RPG applications submitted by the same PIs more than 12 months but less than 5 years after parent grants.
- 161 matched pairs from 124 parent grants were identified, and then confirmed by Program Administrators.
- 50 of the 161 matched pair RPG applications were ultimately funded.

So the questions for evaluation became: what is the success rate for the "matched offspring" grants, and is that success rate better or worse than the overall NIEHS/NIH RPG success rates?

The matched offspring grants had a 31% (50/161) success rate, substantially higher than the 22% rate for the unmatched grants, 22% NIEHS-wide, and 26% NIH-wide. A further question was whether there was a difference in the success rate of matched offspring grants resulting from solicited vs. unsolicited R03/R21 grants. The data showed that the matched offspring RPG grants that emerged from solicited parent grants were more successful—35% vs. 23%. The comparison for matched offspring R01s was slightly different—33% success for solicited; 30% for unsolicited.

Conversion rates told a similar story, Mr. Phelps reported. The R03 offspring applications were more likely to be funded than offspring applications from R21s (45% vs. 33%).

In terms of publications, R03 matched offspring grants were found to have generated more publications per grant and more citations per grant. However, R21 matched offspring grants had a slightly higher impact factor.

To gather data about the status of new investigators with these grants, the group analyzed the 386 investigators and determined that 179 (46%) could be considered to be new investigators. Of the 179, 83 (46%) had been awarded an NIH grant after the R03/R21. The data showed that 78%, 300/386, were new investigators to NIEHS. Of that group, 62 (21%) subsequently received an NIEHS grant. Thus, 62 new investigators were brought into the NIEHS family through these small grant mechanisms.

The group concluded that:

- R03 and R21 grants are effective at stimulating more complex RPG applications and awards
- Productivity of small grants, measured by publications, is impressive
- Given that RPGs resulting from previously funded R03 or R21 grants had a higher success rate (31%) than those without a previous small grant history (22%), it is recommended that NIEHS continue its investment in small grant mechanisms.

Dr. Birnbaum thanked Mr. Phelps, adding that the data would be valuable in deciding to continue to invest in small grants as a way of helping to accomplish the current budgetary goals being pursued.

Consideration of Grant Applications

At the end of the afternoon session on February 16, 2011, Council went in to closed session to discuss applications that were under consideration for this Council Round. 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).

Dr. Birnbaum reported to Council the results of the internal "PULSE" survey that had been conducted in November 2010. Staff participation was 80%, and of those respondents, 91% said that NIEHS was "a good place to work."

XXII. Adjournment

Dr. Birnbaum thanked Council for its efforts and officially adjourned the meeting.

The meeting was adjourned at 2:18 p.m. on February 17, 2011.

CERTIFICATION:

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

_____ _____

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

Gwen W. Collman, PhD
Executive Secretary
National Advisory Environmental Health Sciences Council

Attachment:
Council Roster