

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

**MINUTES OF THE ONE HUNDRED FORTY-EIGHTH MEETING OF THE
NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL**

May 24-25, 2016

The National Advisory Environmental Health Sciences Council convened the open session of its one hundred forty-eighth regular meeting on May 24, 2016 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. The closed session of the meeting was held May 25, 2016.

The meeting was open to the public on May 24, 2016 from 8:30 a.m. to 4:30 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 May 25, 2016 from 8:30 a.m. to 11:00 a.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*.

Dr. Linda Birnbaum presided as Chair.

Participating Council Members

Habibul Ahsan, MD (by telephone)
Philip Brown, PhD
William Cibulas (*ex officio*) (by telephone)
Jeanne Conry, MD, PhD (by telephone)
Irasema Coronado, PhD
David Eaton, PhD (by telephone)
Kevin Elliot, PhD
Brenda Eskenazi, PhD
Kenneth Fasman, PhD (by telephone)
Andrew Feinberg, PhD
Tomás Guilarte, PhD
Della Hann, PhD (*ex officio*)
James Johnson, Jr., PhD (*ex officio*)
Norbert Kaminski, PhD
Maureen Lichtveld, MD
José Manautou, PhD
Donna Mendrick, PhD (*ex officio*)
Marie Lynn Miranda, PhD

Avrum Spira, MD (by telephone)
Viola Waghiyi
Deborah Winn, PhD (*ex officio*)

NIEHS Staff

Kathy Ahlmark
Janice Allen, PhD
Robin Arnette, PhD
David Balshaw, PhD
Martha Barnes
Bryann Benton
Linda Birnbaum, PhD
John Bucher, PhD
Jed Bullock
Danielle Carlin, PhD
Lisa Chadwick, PhD
Jennifer Collins
Gwen Collman, PhD
Caroline Dilworth, PhD
Christina Drew, PhD
Lisa Edwards
Symma Finn, PhD
Christine Flowers
Barbara Gittleman
Kimberly Gray, PhD
Virginia Guidry, PhD
Janet Hall, MD
Astrid Haugen
Michelle Heacock, PhD
Jerry Heindel, PhD
Heather Henry, PhD
Jon Hollander, PhD
Chip Hughes
Michael Humble, PhD
Bill Jirles
Laurie Johnson
Raja Jothi, PhD
Bonnie Joubert, PhD
Helena Kennedy
Alfonso Latoni, PhD
Cindy Lawler, PhD
Kelly Lenox
Chris Long
Robin Mackar
J. Patrick Mastin, PhD
Steven McCaw

Rose Anne McGee
Liz McNair
Mark Miller, PhD
Sri Nadadur, PhD
Sheila Newton, PhD
Aaron Nicholas
Liam O'Fallon
Kristi Pettibone, PhD
Jerry Phelps
Nicole Popovich
Molly Puente
Les Reinlib, PhD
Elizabeth Ruben
Thad Schug, PhD
Carol Shreffler, PhD
William A. Suk, PhD, MPH
Kimberly Thigpen Tart, JD
Claudia Thompson, PhD
George Tucker
Fred Tyson, PhD
Michelle Victalino
James Williams
Rick Woychik, PhD
Demia Wright
Darryl Zeldin, MD

Members of the Public Present

Ernie Hood, Bridport Services, LLC
Joanna Matheson, PhD, CPSC
Mike Phillips, RTI International
Trey Thomas, PhD, CPSC
Mark Zylka, PhD, UNC-Chapel Hill

I. Call To Order and Opening Remarks

NIEHS/NTP Director and Council Chair Linda Birnbaum, Ph.D., welcomed attendees and called the meeting to order. She welcomed new Council members Drs. Coronado, Lichtveld, Manautou, and Spira, and Dr. Lauren Zeise, who was unable to attend. She asked all present in the room to introduce themselves, which they did. She asked the Council members attending by telephone to introduce themselves. Following the introductions, NIEHS Division of Extramural Research and Training (DERT) Director and Council Executive Secretary Dr. Gwen Collman reviewed meeting logistics, including the voting process.

II. Review of Confidentiality and Conflict of Interest

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

III. Consideration of February 2016 Meeting Minutes

Approval of the February 2016 meeting minutes was moved and seconded, and Council voted unanimously to approve the minutes. Dr. Collman noted the dates of the upcoming Council meetings for members to put on their calendars.

IV. Report of the Director, NIEHS

Dr. Birnbaum updated Council on Institute developments since the February 2016 Council meeting.

She began with a report on appropriations. She said that she was guardedly optimistic regarding the budget, observing that "Hopefully, we'll be at least even with where we were last year, and maybe if the stars align, we'll be a little bit ahead." She reviewed several other activities in her legislative report, including congressional briefings on endometriosis and bisphenol A. She noted that it appears that TSCA reform will pass in this session of Congress.

Turning to science advances, Dr. Birnbaum briefly summarized several recent publications by NIEHS/NTP personnel or grantees. She began with a "One NIEHS" study involving multiple NIEHS divisions and external groups that employed a genome-wide consortium meta-analysis to look at DNA methylation in newborns and maternal smoking in pregnancy. She also provided short synopses of recently published studies from DIR, DNTP, and DERT researchers.

She outlined the upcoming events related to the NIEHS 50th anniversary, including the main event at NIEHS November 1.

Dr. Birnbaum described recent NIEHS news items and highlights, including several ongoing efforts related to the drinking water crisis in Flint, Michigan. She updated staff developments such as new hires, promotions, retirements, and recruitments. She described recent visits to NIEHS by former *ex officio* council member Dr. Yvonne Maddux, the Vice President for Research at the Uniformed Services University, and Dr. Janine Clayton, Director of the NIH Office of Research on Women's Health (ORWH).

She recounted several examples of successful NIEHS involvement in environmental health sciences training, which has been the case over the institute's 50 years. She noted that the total current NIEHS/NTP investment in training is \$28.1 million.

She completed her presentation by detailing the five new ONES (Outstanding New Environmental Scientist) program awardees for 2016.

Responding to a footnote in Dr. Birnbaum's appropriations graphic, Dr. Kaminski asked her about NIEHS/NTP involvement in AIDS research. She described several research programs related to AIDS/HIV. Dr. Bucher discussed NTP studies looking at combination AIDS therapeutics. Dr. Zeldin added a comment about NIEHS studies. Dr. Birnbaum said that a new head of the NIH AIDS programs had recently been announced.

V. Report of the Director, DERT

Dr. Collman updated the council on activities and developments within DERT since the last meeting in February.

Responding to a question raised by Dr. Eaton in the February meeting, Dr. Collman provided a breakdown of Research Project Grants (RPG) spending, which showed that NIEHS spends considerably more on unsolicited RPGs than on solicited RPGs.

She briefed council members on the potential impact on postdocs from the new rule on overtime pay in the Fair Labor Standards Act, which will take effect in December. With a new threshold for exempt status, that is, non-eligibility for overtime, many postdocs with 0-3 years of postdoctoral experience employed on NRSA and RPG grants would be below the new recommended threshold of \$47,476 and thus could be eligible for overtime pay. Over the next few months, NIH will be in communication with the Department of Labor on the potential impact of the change on grantee organizations. NIH plans to increase support for NRSA stipends in FY 2017 so that all postdoctoral NRSA recipients are at or above the exemption threshold. Extramural institutions can decide whether to raise salaries of postdoctoral employees to the new NRSA levels or to permit paid overtime to those earning less than the threshold. Dr. Collman said that NIH should soon be issuing guidelines to help universities with the transition. "The NIH will work together with the universities to implement these changes as smoothly as possible," she said.

Council members discussed the developments. Dr. Kaminski said it was his impression that the universities would need to make up the difference in salary if they choose to take their postdocs up to the threshold level. Dr. Collman replied that NIH has not worked out the financial implications yet, but is actively modeling and projecting to see how increases will affect the training budget. She added that universities will need to

work out a strategy for complying with the new rule, and by the end of the fiscal year the NIH guidance should be released to help with the transition. Dr. Kaminski reiterated the concern that universities would have to make up the difference to remain in compliance, particularly since “it would be very impractical to try to keep track of overtime hours.” Dr. Birnbaum noted that many universities would likely be obligated to pay overtime or increase the salary base. Dr. Miranda speculated that perhaps NIH was not planning any adjustments to awards to postdocs on non-training grants. Dr. Collman agreed that at this time NIH is concentrating on training grant postdocs. Dr. Lichtveld noted that for most academic institutions, the academic year starts in July, making it difficult for them to proactively deal with the change, particularly with regard to the non-training grant postdocs. Dr. Collman said that NIH is aware of that issue, and program staff will be prepared to discuss issues at individual universities as the changes approach.

Dr. Collman continued her presentation by describing a new environmental health economics resource, in alignment with NIEHS Strategic Plan Goal #10. The resource – the Environmental Health Economics Analysis Annotated Bibliography – is a searchable database that summarizes key attributes from more than 70 environmental health science articles that include an economic impact component. The Goal 10 web page is also in the process of being updated to include highlights from NIEHS-funded projects that incorporate an economic component.

She provided a summary of highlights from Grants Management Branch and Program Analysis Branch activities since the February Council meeting, along with grantee meetings during that period. She summarized DERT highlights from scientific meetings in FY 2016, and recapped 2016 Keystone Science Lecture Seminar Series lectures along with upcoming lectures. She also described several ongoing NIEHS webinar series, as well as the PEPH podcast series. PEPH is adopting a coordinated communication approach focusing on healthy families, healthy spaces, and healthy communities.

She announced the Environmental Health Science FEST (Facilities, Engagement, Scientific advancement, and Training), a grand meeting of NIEHS grantees to be held December 5-8, 2016 as part of the NIEHS 50th anniversary celebration.

Dr. Feinberg suggested reaching out to the editorial community for coverage of the EHS FEST. “This is something that really deserves a lot of attention,” he said.

Dr. Brown suggested several resources that may not have been captured originally in the economics bibliography. Dr. Collman pledged to look into his suggestions and possibly expand the database.

VI. Presentation by Pioneer Awardee: Genetic and Environmental Risks for Autism

Dr. Mark Zylka, a 2013 NIH Director's Pioneer Award winner, was recently appointed director of the UNC Neuroscience Center at UNC-Chapel Hill and is partially funded by NIEHS.

Dr. Zylka described his laboratory's work on identifying the genetic and environmental factors associated with autism. Hundreds of genes have been linked to autism, but his group has focused on a single gene, *Ube3a*. Deletion of *Ube3a* causes the neurodevelopmental disorder, Angelman syndrome, while duplication or triplication of the gene is linked to autism. These genetic findings suggest that the ubiquitin ligase activity of *Ube3a* must be tightly maintained to promote normal brain development. Zylka's group found that protein kinase A (PKA) phosphorylates *Ube3a* in a region outside the catalytic domain, at residue T485, and inhibits *Ube3a* activity toward itself and other substrates. The research identifies PKA as an upstream regulator of *Ube3a* activity and shows an autism-linked mutation disrupts this phosphorylation control. The findings also implicate excessive *Ube3a* activity and the resulting synaptic dysfunction in autism pathogenesis. Environmental factors, including pesticides, have been linked to autism and neurodegeneration risk using retrospective epidemiological studies. Zylka's team sought to prospectively identify chemicals that share transcriptomic signatures with hundreds of chemicals commonly found in the environment and on food. They found that rotenone, a pesticide associated with Parkinson's disease risk, and certain fungicides, including pyraclostrobin, trifloxystrobin, famoxadone, and fenamidone produce transcriptional changes *in vitro* similar to those seen in brain samples from humans with autism, advanced age, and neurodegenerative disorders such as Alzheimer's disease and Huntington's disease. Those chemicals stimulate free radical production and disrupt microtubules in neurons, effects that can be reduced by pretreating with a microtubule stabilizer, an antioxidant, or with sulforaphane. Zylka's research provides a way to prospectively identify environmental chemicals that transcriptionally mimic autism and other brain disorders.

Dr. Birnbaum asked Dr. Zylka for his thoughts on the potential interaction between use of pesticides, fungicides, and herbicides in Brazil and the occurrence of microcephaly in babies born to mothers carrying the Zika virus. He said that his type of work could be used to identify chemicals that affect neurons and to assess the impact of Zika on cultures, but that he did not have access to the virus at this point.

Dr. Feinberg suggested that epigenetics is relevant to Dr. Zylka's work, particularly in epigenetic changes in the father that could be transmitted to the offspring, particularly changes in DNA methylation. Dr. Zylka acknowledged that that could be a fruitful avenue to pursue.

Dr. Guilarte asked about the images of dendritic spines Dr. Zylka had shown, and wondered whether the changes illustrated had been characterized. Dr. Zylka said that they had looked at all parameters associated with spines, but they had not run electrophysiological tests, and so could not say anything about function at this point. Dr. Guilarte asked about the TSPO gene, and Dr. Zylka said there was interest in the gene.

Dr. Eskenazi mentioned her epidemiologic study that showed relationships with organophosphates, and asked Dr. Zylka if he had considered looking at the fungicides with OPs, and whether his model allowed looking at more than one chemical class at the same time. He replied that his group is definitely interested in looking at combinations, using the assay to look at the commonly used mixtures.

Dr. Bucher mentioned that NTP had been looking at a larvacide in use in Brazil, and had found that of the roughly 20 nuclear receptors examined, it affects 6 or 7.

Dr. Lichtveld noted that for mixtures, the most could be learned from the lower- and middle-income countries, where they are often in use. She said that in a country with no environmental policies in place, Surinam, a higher level of depression is being seen in agricultural workers, and that pesticide ingestion is being used to commit suicide.

Dr. Coronado said that much of our food is imported, and so there is no data regarding the use of fungicides and pesticides in other countries and how that might correlate with health effects in the U.S.

Dr. Kaminski asked whether Dr. Zylka had looked into compounds of abuse such as opioids and cannabinoids, and whether there might be any linkage with autism in terms of PKA action. He said they had not looked at drugs of abuse specifically, but had looked at some generic modulators of PKA. He said it is thought that phosphorylation modulation could be used to treat duplication of 15q, which is a very common form of autism. He said the problem is that there are no good mouse models of that condition at present, but that one of his colleagues is developing one.

VII. Oceans and Human Health Concept

Dr. Frederick Tyson presented a concept clearance developed to continue NIEHS support of Oceans and Human Health (OHH) research programs through solicitations. The proposed programs will add emphasis on climate change to keep pace with emerging marine and lacustrine environmental health challenges.

He provided background information on the history of the NIEHS partnership with the National Science Foundation in OHH research (which began in 2004), why NIEHS

supports OHH and Great Lakes research, and the impacts of the past programs in the area.

The NIEHS and NSF are pursuing support for an additional round of collaborative funding of Oceans and Human Health through the Centers for Oceans and Human Health 3 (COHH3). The purpose of the COHH3 program is to provide linkages between marine scientists and biomedical investigators in order to support interdisciplinary research in areas where improved understanding of marine/lacustrine processes and systems has potential to reduce public health risks and enhance existing biomedical capabilities. A new focus of this multi-disciplinary research program would be on how climate change is projected to increase risk to human health as a consequence of: rising sea levels; ocean acidification; increasing frequency and intensity of severe weather events; failed or compromised infrastructure; changing hydrology; warmer ocean temperatures, decreased water volume in the Great Lakes Basin; increased duration of toxic bloom events leading to longer windows of opportunity for exposures to HAB toxins, as well as altered patterns of sediment distribution.

Dr. Tyson noted that NIEHS intends to commit \$3 million/year and the NSF intends to commit \$4 million/year for 5 years to support 5-7 centers.

The COHH3 P01 RFA will require a multidisciplinary approach, with multiple research projects (at least 3, with one or more focused on climate change), a community engagement component, and an administrative core. The concept also calls for a separate Program Announcement with Review to solicit R01 research activities relevant to OHH.

Dr. Eaton was the first Council reviewer. He said the program is very important, and that the concept as presented made a lot of sense as a worthy follow-on to past NIEHS investments in OHH research. He said he was pleased to see that a reasonable amount of money had been committed. He approved of the community outreach component and the partnership with NSF.

Dr. Miranda was the second Council reviewer. She agreed that it is an important program with a creative mechanism put into place that will help advance the science. She endorsed the emphasis on climate change as "a great addition to the program." She also approved of the inclusion of Great Lakes research in the program. She said she liked the combined P01/R01 approach. She suggested that the program include outreach to the state and local agencies where innovative climate change work is taking place. She also suggested that it would further strengthen the program to include NOAA. She said that the RFA should include reference to the importance of maintaining the integrity of the Great Lakes in terms of drinking water.

Dr. Eaton agreed with Dr. Miranda's point about NOAA, particularly in terms of its work in harmful algae blooms. He asked if there had been any discussions with NOAA about the RFA. Dr. Tyson said that there have been interactions with NOAA, particularly on climate change, but that it cannot be a funding partner due to differences in funding practices. Dr. Miranda emphasized that NOAA grantees should be invited to NIEHS grantee meetings.

Dr. Tyson agreed that the RFA should include language encouraging interaction with state and local-level partners.

Ms. Waghiyi encouraged collaboration with indigenous people with knowledge of traditional ecologies.

Dr. Manautou asked what the current philosophy would be about receiving grant applications from multiple investigators who may not have a record of working together, but have the range of expertise called for in the program. Dr. Tyson said that reviewers would probably not look favorably when investigators have not worked together in the past, as opposed to those who have collaborated previously. He noted that preliminary data would strengthen the review. Dr. Collman added that NIH does offer a multi-PI designation in situations where multi-disciplinary expertise is needed.

Dr. Litchveld mentioned that hundreds of millions of dollars are currently being funneled to the Gulf States, virtually all of which is targeted to ecosystems research, not human health research. She suggested strengthening the RFA to add emphasis to the human health research aspect. She also suggested that drought be included as an impact of climate change in the proposal. Dr. Miranda added that a few years ago there was a drought in the Great Lakes area that changed the ecosystem, as one example of climate change-induced drought affecting lacustrine and ocean health.

Dr. Elliott asked whether there was a vision for how tight the integration should be among the multiple disciplines involved; whether they would work in their specialties or work directly together. Dr. Tyson replied that the program would have the flexibility to accommodate either approach.

Dr. Collman called for a motion and second to support the concept, which were made. The Council voted unanimously to approve the concept.

VIII. Why Not to Look under the Lamppost: A Case for Looking Elsewhere

Following an introduction by NIEHS Science Director Dr. Darryl Zeldin, Dr. Raja Jothi, Senior Investigator in the Systems Biology Group, briefed the Council on his research.

Jothi's group seeks to describe developmentally and environmentally responsive gene networks in embryonic stem cells (ESCs). They have shed light on many genes and pathways with previously unknown roles in ESC biology, and have helped to connect the dots for a better understanding of how signaling and transcription cascades instruct epigenetic and transcriptional programs controlling cell fate decisions such as whether or not to differentiate. The findings will contribute to learning about how ESCs can be used as effective model systems for regenerative medicine, disease modeling, and toxicity/drug testing.

Dr. Kaminski asked whether Dr. Jothi felt that the current bioinformatics tools are robust, and whether he would support expending more resources to expand them based on his type of work. He also asked Dr. Jothi if he felt that the quality control in the various databases he uses is adequate. Dr. Jothi replied that a biologist would probably say that there are not enough bioinformatics tools to address basic questions. However, he noted, bioinformaticians only develop tools based on expressed needs. He noted that not all of the big data available is "clean." His group integrated data from 70 different studies, with a process for weeding out false positives.

Dr. Spira said he appreciated Dr. Jothi's computational approach combined with wet bench validation. He noted that most groups are now moving from ESCs to induced pluripotent stem cells, and asked Dr. Jothi if he had looked at gene networks in those cells. Dr. Jothi replied that other labs have shown that at the level of gene expression profiles there is not much difference between the two stem cell types. Dr. Spira asked if Dr. Jothi if he had looked at publicly available data sets looking at various environmental exposures and gene expression responses in epithelial cells or other cell types and seen some of the networks he had described recapitulated in differentiated cells. Dr. Jothi said his lab had not yet done so, but plans to make that their next step, particularly breast cancer stem cell models and exposure data sets.

Dr. Manautou asked about progress in Dr. Jothi's work with mouse models. Dr. Jothi noted that his group is very small, with one postdoc currently using mouse models that develop spontaneous breast tumors, exploring the process of metastasis. Another project looks at enhancers, he added.

IX. NIEHS-CPSC Supported Center for Safety Implications for Nanotechnology in Consumer Products

Dr. Sri Nadadur presented to Council a concept to support a U54 center for safety implications of nanotechnology, a collaborative effort between NIEHS and the Consumer Product Safety Commission (CPSC). The CPSC currently lacks a mechanism for obtaining reliable data on identifying new products containing nanomaterials, and information on consumer use and interaction with such products

that are already on the market. The hope is that the center will aid in filling the research gaps to develop a rational and scientifically guided, risk-based approach to address potential health concerns associated with exposure to consumer products containing engineered nanomaterials (ENMs), which have increased from 54 products in 2005 to 1814 products in 2014.

The multidisciplinary, multi-project center will address four key knowledge gaps:

- Types and characteristics of ENMs in consumer products
- Real-world use and lifecycle of products to assess human exposure
- Inventories of diverse consumer products to understand factors (physical, human and environmental) affecting release of ENMs and associated public perception
- Human exposure assessment

The center will also have one administrative core and an analytical support core. There will also be an external advisory committee composed of NIEHS and CPSC scientific officers.

The CPSC has requested \$2 million as part of its Healthy Children Initiative in the FY 2017 budget to fund the new nanotechnology center with NIEHS.

Dr. Fasman was the first Council reviewer. He said he was very supportive of the concept. He said it is a logical and natural extension of NIEHS's current activities in studying ENMs, and a "clear win" for extending CPSC's ability to oversee this rapidly evolving area of technology. He was unclear about the extent of the center's involvement in inventorying ENMs in consumer product. Dr. Nadadur said the center would compile, release, and distribute information in addition to the testing data. Dr. Thomas from the CPSC added said that since his agency does not have pre-release regulatory approval, it is constantly trying to understand where the market is going, the materials that are being used, and the products into which they are being incorporated. He said the agency has established an internal database, but more information is needed, and the center would assist in that. Dr. Fasman asked about plans for the center's administrative core, specifically about combining its community engagement activities with the core. Dr. Nadadur felt that it was a practical plan, but that it could change once they begin writing the RFA.

Dr. Eaton was the second Council reviewer. He was also supportive, although it is a bit different from the usual NIEHS pursuit in that there is little biology involved. He said that in the field of nanotechnology, characterizing routes of exposure remains a weak link. Thus, having a center concentrating on real-world exposures is important, but is also a monumental task given the large number and variety of ENMs, lending importance to the inventory aspect. He said that to be effective, the project may require multiple sites, with expertise drawn from different institutions. He asked who might be

the target audience of the RFA, whether it would be academia, industry, contract research organizations, etc. Dr. Nadadur replied that the RFA would definitely be targeted toward the academic community. He added that it will be a virtual center, rather than being located in one place. Dr. Thomas noted that in the CPSC's previous partnerships in this area, a number of universities had been involved, and the center would allow it to go to the next level in terms of tapping existing expertise. Dr. Eaton noted that the RFA should reflect the idea that investigators with different expertise from different institutions should collaborate.

Dr. Mendrick asked whether there is a plan to reach out to collaborate or coordinate with the FDA's two core nanotechnology facilities. Dr. Nadadur replied that NIEHS has existing relationships with the nanotechnology efforts at FDA and there would be efforts to involve both programs in the center's plans.

Dr. Guilarte felt that there would be a considerable challenge working from a consumer product perspective regarding ENMs. He suggested going to the companies making the materials in large quantities, making it easier to develop exposure assessment methods. He asked how internal dose would be addressed. Dr. Nadadur noted that the NTP and NIOSH are collaborating on an ongoing project to look at some of the sites where ENMs are produced, using some of the existing tools to assess exposure levels. He added that methods to assess internal dose are under development and that is a focus of the NHIR program which is being funded this summer.

Dr. Collman noted that a few years ago there was a workshop on human exposure to nanomaterials, where many issues had arisen related to ENMs in consumer products. She said that it would be good to be able to take some of the research needs identified then and partner with CPSC on a project to explore those questions.

Dr. Elliott said it would be tricky to identify the relevant communities and stakeholders, so more expertise would be needed to do the community engagement well, which could be an argument for separating it out, as Dr. Fasman had suggested. He said that the research on consumer awareness and perception might also need to take place at a separate institution. He noted that the NSF centers for nanotechnology and society might be able to feed into or inform the center's work.

Dr. Brown seconded the idea that the community engagement aspect should be its own core. He suggested that there could be many fruitful collaborations working with CPSC. He also suggested that the center engage with environmental health and safety departments at universities to measure ENMs in laboratories.

Dr. Bucher described the NTP's work looking at the difference in toxicity between nano-level silver and bulk silver, where there appears to be little difference in the effects of exposure.

Dr. Coronado asked if OSHA was involved in the research. Dr. Nadadur said that it is, as is NIOSH. Dr. Coronado asked about ENMs in products coming into the U.S. from other countries. Dr. Thomas noted that CPSC has an interagency agreement with NIOSH. He said that CPSC has been proactive about foreign products, particularly children's products, coming from overseas. He added that assessing risks of exposures to such products is one reason the proposed center is so important. Dr. Coronado said that communication of risk information would be vital to the effort. Dr. Collman confirmed that that would be part of the community outreach aspect of the program.

Dr. Birnbaum thanked the CPSC for their interest in working with NIEHS, noting that the center is a good example of cross-agency collaboration.

Dr. Collman requested a motion and second to approve the concept, which were made. The council voted unanimously to approve the concept.

**X. People not Projects: The NIEHS R35 Mechanism –
Revolutionizing Innovative, Visionary Environmental health Research (RIVER)**

Dr. David Balshaw, chief of the Exposure, Response, and Technology Branch, briefed the Council on the new R35 funding mechanism.

NIH has developed a new Research Project Grant mechanism, the R35, which is intended to fund people, not projects, and reward researchers with a broad vision and track record of impactful research with increased scientific flexibility and stability in funding. NIH has granted individual ICs flexibility in adapting the R35 mechanism to their individual mission and priorities within the following guidelines:

1. The PI must devote a minimum of 50% research effort to the project, and
2. The PI may request up to \$750,000 in direct costs annually, for a maximum of 8 years.

Each of the five ICs that have released R35 programs to date has implemented the mechanism in a distinct way, and NIEHS will implement its program based on lessons learned. It will seek to identify those individuals within the grants portfolio who are most likely to benefit from a flexible research program and sustained effort to push their research in new and important directions. It is not career stage-specific, but will particularly encourage mid-career investigators. Also, it will not target specific scientific areas but will encourage exploration in all areas supported by NIEHS.

To decrease impact on the overall budget, the program will require consolidation of existing awards into the R35 award, within certain parameters. The R35 award would be the total of the consolidated awards plus a 10% "bump-up," to encourage exploratory activities. However the new award could not exceed \$750,000 in direct. The proposed

R35 will initially be a six-year award, with a program review in year 5 to award years 7 and 8. Dr. Balshaw delineated several scenarios based on the proposed requirements.

RIVER is a pilot program to be updated and renewed annually. A total of 5-6 awards will be made each year, at a proposed cost of \$6 million per year, which will largely be offset by consolidation and relinquishment of existing awards. It is anticipated that the RFA will be released in July, 2016, with funding to begin July, 2017.

Dr. Guilarte was the first Council reviewer. He said he welcomed the program, with its obvious benefits to researchers, such as flexibility to engage in high-risk research. He expressed concern about the perception that the program would target a particular age range with the emphasis on mid-career investigators. He also wondered what would happen after an R35 grant ends, and asked whether the grant was intended to be renewable, and if so how many times. He also inquired about the potential effect on the R01 payline, which could be significant.

Dr. Feinberg was the second Council reviewer. He said he was very enthusiastic about the idea, but had some concerns. First, looking at the chart of how the other ICs had implemented the mechanism, he felt that some of them were quite specific to their areas. For example, for the National Institute of Dental and Craniofacial Research's program, the targeting of mid-career investigators was intended to retain researchers in the field. He said he did not agree with the mid-career focus for NIEHS, in that the emphasis should be on the creativity rather than on age. He also felt that the nomination process, with two per institution, was too restrictive. He disagreed with the 6-year with 2-year review design, and recommended a straight 7-year award duration.

Dr. Balshaw clarified that the program is not specific to the mid-career stage but noted concern from NIEHS program staff that mid-career investigators will require particular encouragement to seek support through the program. Dr. Guilarte said there would be no problem getting applications from people in any stages of their careers. Dr. Collman noted that the program would be limited to people with current grants, and so is not meant to be an open solicitation. Dr. Balshaw said that although the program is a pilot at present, if it goes well the intention would be for it to be a renewable award. In any case, as designed, there would be ample time for an investigator to apply for an R01 when the end of the R35 is approaching.

Dr. Miranda asked whether the roll-out would result in solicitations in 2017, 2018, and 2019. Dr. Balshaw said that was a question where Council input was wanted, but the ability to issue 3-year RFAs does exist at this point, or it could be done as a one-year RFA, to be revised based on response. Dr. Miranda asked if the specific aims associated with grants that are consolidated under the R35 would simply go away. Dr. Balshaw replied that the projects themselves go away and the aims would be

incorporated into the R35 project. Dr. Miranda commented that it should be clearly stated that the program will be offered in multiple years, because investigators with R01s are often funded for several years, so some of the most creative researchers might not become eligible for some years. She also mentioned that the 50% requirement, along with not applying for any investigator-initiated awards, could leave some investigators hanging in terms of their ability to cover the other 50% of their salary and to cover graduate students or postdocs they might want to support. She recommended reconsidering the prohibition against applying for new investigator-initiated awards, taking into account people who are on soft money. She added that if original specific aims go away, she would worry about the graduate students and postdocs supported on those project, as would good investigators, who would take a few years to transition to the new program, because they will not forsake their graduate students and postdocs. Dr. Balshaw noted that the specific aims do not themselves go away, but they become the R35. The project ends, but the science continues.

Dr. Manautou asked Dr. Balshaw if he his analysis had shown the potential ratio between senior and mid-career investigators. Dr. Balshaw said there were both, in some cases from the same institution. Dr. Manautou asked if the elements of the written document would be different because the program is more investigator-centered than focused on specific aims. Dr. Balshaw confirmed that the emphasis is on ideas and innovation, similar to how different the application for a Pioneer Award is to an R01 application. Dr. Feinberg said that in the Pioneer Award, there can be clear aims but one is not held to specifics. He noted that the applicant must write about him/herself, which many scientists are uncomfortable with.

Dr. Litchveld asked Dr. Balshaw if he had consulted with academic institutions when planning the program. Dr. Balshaw said he had not done so formally, although there had been some conversations. Dr. Collman noted that the concept had been preceded by a six-month-long working group across NIH, with feedback regarding other model groups. She added that the purpose of the current discussion was to get feedback from the extramural community. Dr. Litchveld said she worried about investigators who have already been successful but may find themselves in a difficult position approaching the end of an R35.

Dr. Eskenazi said she felt that the dollar amount for the grants put epidemiologists at a disadvantage, since they tend to have larger R01s. Also, she noted that a substantial amount of salary would need to be covered by the funding, again, putting epidemiologists and investigators with hard money at a disadvantage. Dr. Balshaw noted that the 50% requirement addresses research effort, without reference to administrative effort. He said that his group had spent much time considering the epidemiologist question, and hoped that cohorts could be supported largely through a cohort maintenance program, giving the epidemiologist the resources to move their

science forward. Dr. Eskenazi noted that that did not cover everyone doing epidemiological research.

Dr. Eaton said he was concerned about the potential institutional limitations, which could artificially limit the science and be unfair to those at larger institutions. He recommended removing that limitation. He felt that NIEHS would not be overwhelmed with applications. He asked if the limitation on R01 applications applied only to NIEHS or across NIH. Dr. Collman replied that it was only NIEHS.

Dr. Kaminski agreed with Dr. Feinberg's suggestion to make the award a straight 7 years. He felt that they should not be renewable.

Dr. Miranda asked if the NIH Pioneer awards are renewable, and whether investigators with Pioneer awards are allowed to apply for others. Dr. Feinberg said they are not renewable, and other applications are allowed.

Dr. Guilarte said he assumed that once an R35 had expired, the investigator would be allowed to re-enter the R01 pool. Dr. Collman noted that the renewal status of an R35 is up to the individual IC.

Dr. Collman called for a motion and second to approve the concept. The Council voted unanimously to approve the concept.

XI. Worker Training Program (WTP) Ebola Biosafety & Infectious Disease Response Training UH4 Program

Chip Hughes, Director of the NIEHS Worker Training Program (WTP), briefed the Council on the new awards that had just been funded to support the Ebola Biosafety and Infectious Disease Training Response Program.

He provided background information about the WTP, including its components and its past role in infectious disease response training. He delineated the genesis of the Ebola biosafety training initiative, which began its operations in 2014. The current round of eight awards resulted from an extensive gap analysis and needs assessment conducted in 2015. Given what was learned, the WTP invited applications for cooperative agreements to support the development and implementation of occupational safety and health and infection control training programs for workers who may be at risk during infectious disease outbreaks. The project will run from June 2016 until May 2019, and will be comprised of awards totaling \$3 million per year for 3 years, or \$9 million altogether. The programs will focus on dissemination of environmental infection control and hazard recognition training within a broad set of occupational and community settings, including healthcare and non-healthcare sectors. The training program will reach an estimated total of 45,000 workers in 37 states.

Dr. Litchveld asked how the various programs would integrate to form a whole for the next viral outbreak, such as Zika. She also asked whether any of the grantees were involved in training health workers globally. Mr. Hughes noted that the program designers tried to “take a step back” and think beyond Ebola. He agreed that integrating the different institutions involved would be a challenge, as would be trying to integrate a domestic initiative with a global initiative. He noted that it was particularly difficult to conduct research in the midst of a global crisis.

XII. Open Council Discussion

Dr. Collman introduced the final session of the meeting, which was dedicated to an open Council discussion. With Council feedback, it was decided to focus the discussion on the Precision Medicine Initiative (PMI) and the Cancer Moonshot Initiative (CMI).

Dr. Feinberg began the session with some thoughts about the two programs and how they might relate to NIEHS. Although the specifics are confusing, he said, the PMI’s website mentions both prevention and environmental influences on disease, both of which relate directly to the NIEHS mission. He said it seems like an ambitious program, and it should be ensured that it will include elements important to NIEHS such as environmental exposure and epigenetics. He noted that epigenetics, for example, are clearly related to cancer, diabetes, and the microbiome. He found the CMI even more confusing. He observed that in that case as well, environmental exposures and epigenetics should be included, as should prevention, which is related to 80% of cancer. The CMI website says it seeks to accelerate the potential of combination immunotherapy. Another page seeking comments included prevention, but there are just a few there. He asked how elements important to NIEHS can be brought into both initiatives. He noted that it is still early enough to make a difference.

Dr. Collman agreed that both programs were confusing at present in terms of the information available on line. She asked Dr. Winn, who has been involved with both programs in her capacity at NCI, to add some comments.

Dr. Winn said there are certainly opportunities for the NIEHS community to participate, but agreed that it is hard to parse through the information. Both programs will require strong engagement from the extramural community. In the PMI cohort, a number of RFAs are currently being evaluated and will be awarded in the near future, including one to Vanderbilt University. There is also a communications awardee working to understand the stakeholders involved. Health provider organizations will also be evaluated, as will technologies, which may be an especially fruitful area for NIEHS. She said that NIEHS staff have been involved in working to establish some of the questionnaire content and contributing ideas about geospatial and environmental

perspectives. The cohort has an extramural advisory committee. Both initiatives, she added, have had many organizations providing input through a variety of channels. She described two main activities associated with the Moonshot: a task force, which is an interagency working group working to provide more coordination in Federal government cancer-related activities, and a blue ribbon panel, which is working on research issues. The blue ribbon panel includes extramural people on seven committees: expanding clinical trials, enhancing data sharing, cancer immunology and prevention, implementation sciences, pediatric cancer, precision prevention and early detection, and tumor evolution and progression. The groups are seeking input in any form, and are each being asked to provide two ideas to float forward. So in all, 14 ideas will go to the National Cancer Advisory Board (NCAB) in August, 2016. The NCAB will report to the NCI Director, who will release a final set of recommendations to the public. Staff will be writing RFAs and other funding opportunity announcements in September and October, with release in November, and funds to be award in June or July, 2017. Although a limited number of ideas will be forwarded, it is still a good opportunity to put forth ideas that could take on a life of their own, she observed. She encouraged Council members to use the opportunities to put forward new ideas. She noted that particularly with the Moonshot, Vice President Biden has been insistent about the importance of data sharing, fostering collaboration and non-duplication of efforts, and breaking down siloes.

Dr. Birnbaum said she was concerned about the six topics put forth under the Moonshot, and that although one was prevention, it appears that primary prevention is not being addressed at all, and that clearly the role of the environment and the opportunity it presents to prevent cancer is not being considered. She asked Dr. Winn in that context, "Where do we go?" Dr. Winn said it was important to get the ideas in front of the working groups, who have been told to look at the issues with a broad vision. The hard part for them, she observed, will be to prioritize the ideas and put forth two per group.

Dr. Guilarte said that on March 21, more than 70 deans of schools of public health wrote a letter to Vice President Biden expressing concern that the Moonshot may be undervaluing the role of public health and prevention.

Dr. Eskenazi asked what had been decided about the final ages of the PMI cohort. Dr. Winn said it would start with adults, but the intention is to eventually include the full age range, including children. She said there is a working group to look at the issues surrounding children so that they can be included as quickly as possible. Dr. Eskenazi said she had proposed that the cohort start at age 18, which would include a certain number of pregnant women. She also asked Dr. Winn about questionnaires looking at exposure assessment, and noted that neither she nor any of her colleagues had been asked for that type of information as part of looking at environmental exposure. She

asked how she and her colleagues could provide that information to the PMI, to prevent “re-inventing the wheel” by developing new questionnaires. Dr. Winn said that the staff effort had been to give awardees a bit of a head start, and pilot testing is currently being developed. The program won’t be rolled out until late fall, however, so there is still opportunity for more environmental exposure information to be included. It will be the responsibility of the awardees, under their cooperative agreements. Dr. Eskenazi suggested that they should ask NIEHS for help with exposure assessment and collection of relevant biological samples. Dr. Winn agreed, and said she had brought that up to her group to be sure it would be included.

Ms. Waghiyi spoke about the cancer crisis going on in her community, and pleaded for the health disparities involved to be addressed, as research is not sufficient but meaningful change is needed to protect communities like hers. Dr. Collman agreed that stories like hers are important and need to be included in the development of these big initiatives. She noted that NIEHS has a rich history of working with such communities. She asked Council for advice on how to make the many resources NIEHS has developed over the years come alive so that programs like the PMI “can’t not include them.”

Dr. Birnbaum described the PMI listening sessions that had been held around the country, and said that the environment and environmental health had come up at every one. “But I’m not hearing any discussion of it now, and we certainly have not been reached out to at all,” she noted.

Dr. Miranda said she was on Dr. Collins’ PMI advisory panel, likely due to her interest in social and environmental contributors to outcomes. She said the panel is in the process of putting out a series of white papers, one related to characterization of the physical and social environment in the PMI cohort. She pledged to insert content from the current discussion into her forthcoming commentary on the white papers.

Dr. Eskenazi asked Dr. Miranda if there was a white paper on chemical issues. Dr. Miranda replied that chemical issues would be included in the white paper she had cited, as an aspect of the physical environment. Dr. Eskenazi said that perhaps confusion about the definition of “environment” was a reason NIEHS was not being included. Dr. Litchveld said that typically her group describes “chemical” and “non-chemical” stressors, and that perhaps that would be the appropriate terminology approach for the PMI to take. She recommended that both initiatives look through the lens of community, as opposed to focusing solely on the needs of individuals.

Dr. Brown said that colleagues should be reminded about the existing breast cancer and the environment program, which has a strong community element, with breast

cancer advocacy groups participating. He also mentioned the Interagency Breast Cancer and the Environment Research Committee that was set up by the President, as well as the President's cancer panel from several years ago that issued a report about the environment and breast cancer. Thus, there is a legacy among several federal agencies that should be recalled and incorporated.

Dr. Elliott said that the economic arguments should be included in efforts to ensure that environmental health is included in the programs.

Dr. Miranda added that she was concerned that the importance of population and community health was being overlooked in the PMI. "How do you do personalized medicine at scale?" needs to be addressed, so that population and community health research are not forgotten. She said that the community context is vital, particularly in light of the prevalent chronic diseases that cannot be solved in the exam room, but must be solved in the places where people live and work. "If you fail to take into consideration the environmental context in which people reside as well as their social context, we'll never get personalized medicine at scale," she said. Dr. Litchveld agreed that many of the current diseases such as obesity and diabetes must be treated as community problems.

Dr. Birnbaum urged Council members to contact and send information to the appropriate people as referred by Dr. Winn, because more contacts from individuals would help bring attention to the expressed concerns. Dr. Miranda asked Council members to copy her on those communications as well. Dr. Birnbaum emphasized that comments should be addressed to both initiatives. Dr. Winn said that the membership of the Moonshot panel is available on the NCI Moonshot website. Dr. Birnbaum noted that there are several other large initiatives at NIH currently, such as the Alzheimer's Initiative. She urged communication of the growing evidence of a role of the environment in Alzheimer's to the NIA as well. Dr. Feinberg noted that it is "absolutely mandatory" that the executive committees running these initiatives speak to Dr. Birnbaum as they are in their planning stages. Dr. Birnbaum said that NIEHS is more engaged in some of the Common Fund efforts than in some of the other initiatives like the PMI.

Ms. Waghiyi expressed the gratitude of her community to NIEHS, as it has been funding its community-based projects since 2000. She felt, however, that policy and regulatory stances are far behind where the science and traditional knowledge are.

XIII. Adjournment

Dr. Birnbaum and Dr. Collman thanked the open session presenters and the Council members and staff for their participation in the meeting.

The open portion of the meeting was adjourned at 4:30 p.m., May 24, 2016.

XIV. Consideration of Grant Applications

This portion of the meeting (8:30 a.m. – 11:00 a.m., May 25, 2016) 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).

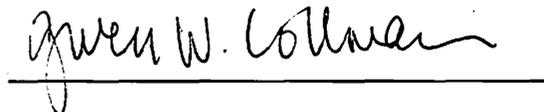
XV. Adjournment

The meeting was officially adjourned at 11:00 a.m., May 25, 2016.

CERTIFICATION:



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