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

MINUTES OF THE ONE HUNDRED FIFTIETH MEETING OF THE NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

February 14-15, 2017

The National Advisory Environmental Health Sciences Council convened the open session of its one hundred fiftieth regular meeting on February 14, 2017 in the Rall Building, Rodbell Auditorium, National Institute of Environmental Health Sciences, Research Triangle Park, NC. The closed session of the meeting was held earlier the same day.

The meeting was open to the public on February 14, 2017 from 10:30 a.m. to 4:45 p.m. and on February 15, 2017 from 8:30 a.m. to 11:30 a.m. In accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), the meeting was closed to the public on February 14, 2017 from 8:30 a.m. to 10:15 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, Jr., PhD (*ex officio*)
Jeanne Conry, MD, PhD (by telephone)
José Cordero, MD (*ad hoc*)
Irasema Coronado, PhD
David Eaton, PhD
Kevin Elliott, PhD
Brenda Eskenazi, PhD
Andrew Feinberg, MD (by telephone)
Tomás Guilarte, PhD
Shuk-Mei Ho, PhD (*ad hoc*)
Norbert Kaminski, PhD
Maureen Lichtveld, MD
José Manautou, PhD
Linda McCauley, PhD (by telephone)
Marie Lynn Miranda, PhD
Donna Mendrick, PhD (*ex officio*)
Susan Schantz, PhD (*ad hoc*)
Andy Shih, PhD (*ad hoc*)

Patrick Sung, PhD (*ad hoc*)
Viola Waghiyi
Deborah Winn, PhD (*ex officio*)
Lauren Zeise, PhD (by telephone)

NIEHS Staff
Janice Allen, PhD
Robin Arnette, PhD
David Balshaw, PhD
Martha Barnes
Linda Bass, PhD
Sharon Beard
Bryann Benton
Linda Birnbaum, PhD
Helena Bonner
Tiffany Bowen
Abee Boyles, PhD
John Bucher, PhD
Danielle Carlin, PhD
Trisha Castranio
Lisa Chadwick, PhD
Pam Clark
Jennifer Collins
Gwen Collman, PhD
Bill Copeland, PhD
Yuxia Cui, PhD
Joanne Damborsky, PhD
Sally Darney, PhD
Christie Drew, PhD
Chris Duncan, PhD
Bryan Duran
Lisa Edwards
Benny Encarnacion
David Fargo, PhD
Katherine Fine
Symma Finn, PhD
Christine Flowers
Amanda Garton
Barbara Gittleman
Kimberly Gray, PhD
Virginia Guidry, PhD
Janet Hall, MD
Alison Harrill, PhD
Astrid Haugen
Michelle Heacock, PhD
Heather Henry, PhD

Jon Hollander, PhD
Michael Humble, PhD
Bonnie Joubert, PhD
Helena Kennedy
Alfonso Latoni, PhD
Cindy Lawler, PhD
Kelly Lenox
Chris Long
Robbie Majors
J. Patrick Mastin, PhD
Kim McAllister, PhD
Steven McCaw
Rose Anne McGee
Liz McMillan
Liz McNair
Carolina Medina
Sri Nadadur, PhD
Sheila Newton, PhD
Aaron Nicholas
Liam O'Fallon
Simone Otto, PhD
Mitsue Parrish
Kristi Pettibone, PhD
Nicole Popovich
Tina Powell
Molly Puente
Steve Ramsey
Lingamanaidu Ravichandran, PhD
Ericka Reid, PhD
Les Reinlib, PhD
Jim Remington
Elizabeth Ruben
Angie Sanders
John Schelp
Thad Schug, PhD
Carol Shreffler, PhD
Ashley Singh
William A. Suk, PhD, MPH
Kimberly Thigpen Tart, JD
Laura Thomas, PhD
Claudia Thompson, PhD
Brittany Trottier
George Tucker
Steven Tuyishime, PhD
Fred Tyson, PhD
Michelle Victalino

James Williams
Scott Williams, PhD
Leroy Worth, PhD
Rick Woychik, PhD
Demia Wright
Darryl Zeldin, MD

NCI Staff
Leah Mechanic, PhD
Gary Ellison, PhD
Wendy Wang, PhD

Members of the Public Present
Polly Armsby, SSS
Maureen Avakian, MDB, Inc.
Ernie Hood, Bridport Services, LLC
Terry Kavanaugh, PhD, University of Washington
Young-Shin Kim, MD, PhD, UCSF
Mike Phillips, RTI International
Richard Rosselli, SSS

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 noted that *ex officio* Council members Drs. Hann and Johnson were unable to attend. She said that Drs. Ahsan, Conroy, Fasman, Feinberg, McCauley, and Zeise would be attending by telephone. She presented retiring Council member, Dr. Tomas Guilarte, with a certificate of appreciation for his service. 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 September 2016 Meeting Minutes

Approval of the September 2016 meeting minutes was moved and seconded, and Council voted to approve the minutes, with all in favor excepting one abstention. 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 September 2016 Council meeting.

She began with a report on budget matters. She reported that there was still ongoing uncertainty regarding the federal budget. NIEHS is operating under a continuing resolution through April 28, and there is uncertainty as to what will happen to the budget after that. She noted that the Common Fund has continued to grow since 2015, while the Superfund appropriation is flat. She discussed the current hiring freeze within the Federal Government.

She described several new laws from 2016 that affect NIEHS, including, notably, the 21st Century Cures Act and the Frank R. Lautenberg Chemical Safety for the 21st Century Act. She provided more detail about the 21st Century Cures Act, which among other provisions authorizes the Precision Medicine Initiative, the Cancer Moonshot, the and BRAIN Initiative. It creates a $4.796 billion roadmap for new federal funds, outside of budget caps, for key NIH initiatives over the next ten years, and establishes an NIH Innovation Account in the U.S. Treasury. She also described the Cancer Moonshot, the Precision Medicine Initiative, and the BRAIN Initiative in more detail. She noted that the NTP is contributing rat and mouse tissue samples from the NTP Archives for a project called "Identifying preventable causes of cancer," which is part of the Cancer Research United Kingdom Grand Challenge competition.

Turning to science advances, Dr. Birnbaum briefly summarized several recent publications by NIEHS/NTP personnel or grantees. First, as an example of "One NIEHS" research, she described a study on the association of arsenic exposure and metabolism with Type 1 and Type 2 diabetes in youth, the SEARCH Case-Control Study. She also provided short summaries of recently published studies from DIR, DNTP, and DERT researchers.

She provided an update on 2016 NTP activities, which included the release of the 14th Report on Carcinogens and several other scientific milestones. She went over the list of 25 clinical research studies currently being conducted at the NIEHS Clinical Research Unit, which are recruiting volunteers. She described recent developments in IT and data science.

In NIEHS news and highlights, she noted several new hires for NIEHS and NTP. She recognized Dr. Michael Fessler as the winner of the NIEHS Scientific Director's Award for Outstanding Intramural Research, and the achievement of NIH tenure by Drs. Xiaoling Li and Raja Jothi. She described several other awards and recognitions garnered by NIEHS and NTP employees and NIEHS grantees.

Dr. Eskenazi asked if the federal hiring freeze applies to the hiring of post-docs at NIEHS. Dr. Birnbaum replied that it does not. Dr. Manautou asked whether it applies to summer fellows. Dr. Birnbaum said that the freeze does not apply to them, but that the situation is fluid in terms of the information being received, and so the answers may be subject to change. Given the anticipated major budget cut for EPA, Dr. Manautou wondered whether the funds for Superfund could be part of that, or considered separate. Dr. Birnbaum noted that there is no cut for EPA yet, but there are proposals for major cuts. The NIEHS funding for Superfund does not come through EPA, but is a separate appropriation, she observed, although it comes through the same committee as EPA's funding. She added that the staffers from that committee have been "extremely positive" over the past few years about the work being done by the Superfund Research Program and the Worker Training Program.

V. The Role of the Microbiome in the Developmental Origins of Health and Disease (DOHaD)

Dr. Lisa Chadwick presented a research concept to the council on the role of the microbiome in the developmental origins of health and disease. The RFA would solicit applications that investigate the potential role of the microbiome in mediating the latent effects of early life exposures. The goal of the RFA is to address key knowledge gaps:

- Determine whether early life exposures to environmental chemicals impact the development and functional capacity of the microbiome
- Establish whether a causal relationship exists between exposure-induced changes in the microbiome and a disease associated with early life exposure
- Investigate persistence of exposure-induced changes to the developing microbiome and the factors that affect persistence
- Determine whether certain developmental windows are more susceptible to long-term changes in the microbiome
- Evaluate the role of the maternal microbiome in transmitting the effects of prenatal exposure to offspring

Appropriate exposures include:

- Environmental chemicals for which early life exposures have been linked to later disease onset, either in animals or in epidemiological studies, even if the chemicals have not yet been linked to changes in the microbiome

- Environmental chemicals that have been shown to cause changes in the microbiome
- Diet, drugs of abuse or smoking (including maternal smoking) in the absence of a relevant environmental chemical exposure are not allowable.

Dr. Chadwick summarized a previous RFA on Environmental Influences on the Microbiome. Of the six projects funded, only one addressed early life. This new R01 RFA would include a budget of $3 million to fund 5-6 grants over 5 years. Projects would be limited to use of animal models, to allow following of exposed individuals across the lifespan. The proposed timeline would include Council review of grant applications in February, 2018.

Dr. Kaminski was the first Council reviewer. He said he felt that the proposal addressed a very important area, as the growing literature is convincing that the microbiome has a very important effect in health and human disease. He said there has been little attention to the effects on the microbiome during early stages of life, and how that may affect later health. He suggested that investigation of indirect effects of environmental factors on the microbiome should be included.

Dr. Manautou was the second Council reviewer. He noted that there is bidirectionality in the host/microbiome relationship. He said he would like to see some clear language in the proposal addressing that issue. He agreed that the subject should be part of the NIEHS portfolio, particularly with so many researchers working in the area. He endorsed the objectives stated in the proposal. He wondered if it might be premature to discuss testing interventions. He felt that the multi-year R01 mechanism was appropriate. He asked Dr. Chadwick about the success of the previous microbiome RFA, which included 3-year R21 projects. Dr. Chadwick described the previous approach. He recommended that the new program should include some justification from the investigators to validate their proposed animal models in terms of their relevance to potential human interactions between the host and the microbiome. He said he was "very enthusiastic" about the subject, overall. Dr. Chadwick said that the project is limited to animal models, although it may include some humanized animal models.

Dr. Birnbaum asked for comments from the Council on the idea of two-phase awards.

Dr. Feinberg expressed concerns about the project. He wanted to ensure that it was not overlapping another microbiome initiative (from OSTP), or the gene-environment interaction initiative to be presented to Council later in the meeting. He felt that there would be a gene sequence dependency to the microbiome interactions, and that it would be "highly overlapping" with the other RFA. He felt that the two concepts could possibly be integrated. Dr. Chadwick replied that it was her understanding that there was no additional NIH funding resulting from the OSTP initiative. She said that her group had extensively catalogued the microbiome research funded by NIH over the past few years. She said that interrelationship of initiatives is often true of any of the science discussed at NIEHS, because it is all related. Dr. Feinberg said that he felt that the proposal was weakened by not considering genetic diversity, and ignoring the genotype is a problem. Dr. Collman thanked Dr. Feinberg for his comments, and noted that use of genetically diverse mouse strains could be added to the scope of the project.

Dr. Lichtveld asked how the research could be anticipatory, as human studies in the area emerge. She asked Dr. Chadwick how the collection of samples could be conducted to anticipate the need for them as human data becomes available, rather than having to start from scratch. Dr. Chadwick felt that was "really great forward thinking," because although there are several early life cohorts in existence, they typically do not have biosamples. She said the key would be to collect samples such as vaginal swabs and/ or fecal samples from infants over several timepoints, in the case of investigating the role of vaginal versus Caesarian births and the microbiome.

Dr. Manautou added that there is also a distinction between hospital and home births in terms of the microbiome. Dr. Birnbaum noted that data suggests that by 2 years of age, the microbiome has "normalized," and the question is whether the difference in the microbiome over those first two years impacts the long-term health of a child. Dr. Chadwick said that there are definitely diseases linked to birth route, but the data in that area are limited.

Dr. Eskenazi said she found the concept extremely interesting, but was also extremely disappointed, because she would like to see humans included. She felt that there are cohorts with the appropriate samples collected. She suggested a smaller RFA soliciting existing human samples. Dr. Chadwick noted that the previous RFA was like that. Dr. Eskenazi said the previous RFA did not focus on developmental windows. Dr. Chadwick agreed, and suggested that researchers may provide unsolicited applications in that area of research in humans. She reiterated that what she really wished to focus on with this RFA was the causal link going from exposure to disease.

Dr. Kaminski said that in his opinion the two-phase approach described by Dr. Birnbaum has merit, with investigators needing to demonstrate some type of milestone achieved before receiving a subsequent infusion of funding.

Dr. Collman asked the Council for a motion and second to approve the concept, which she received. The Council voted 14-1 in favor of the motion.

VI. Up in Smoke: Are There Alternative Facts about Paternal Nicotine Exposure and Risk for ASD?

Dr. Young Shin Kim from the University of California at San Francisco, a child and adolescent psychiatrist, described her research program examining the prevalence and incidence of autism spectrum disorders (ASDs) in a large cohort in her native Korea. She has studied whether the recent dramatic rise of ASD prevalence is a real phenomenon or the result of increased awareness, improved diagnostic methods, and other non-disease factors. She described a new study in the cohort looking at the potential role of paternal smoking in the development of ASDs. She said that the Korean study, along with other prior studies, suggests that paternal smoking is likely to be one of the many toxic chemical exposures that increase risk for ASD. Although the risk is small in and of itself, she noted, when it is added to other potential risk factors, the time is approaching when there is increased understanding of the etiology of neurodevelopmental disorders.

Dr. Eskenazi asked about the question of painkiller use in Dr. Kim's study. She asked for more information about which painkillers were included and their distribution, and whether painkiller use would be looked at in more detail in further studies. Dr. Kim replied that it would, following the planned whole genome sequencing of cohort quartets, which will improve statistical power.

Dr. Eaton noted that the FDA was recently given regulatory authority over e-cigarettes. He asked Dr. Kim her thoughts on studying the cohort of young people using e-cigarettes who would not bring the complications of tobacco smoking. Dr. Kim said it was a very interesting and important question. She described a recent conversation with colleagues in Australia, where apparently using e-cigarettes is not considered "cool," unlike in the U.S., where peer pressure persists. She said the only way to learn about the issue is through gathering evidence and data.

Dr. Cordero asked about how Dr. Kim has been able to define when a child has ASD, given that symptoms may appear at a very early age. He also asked about the possible mechanisms of nicotine leading to autism. Dr. Kim replied that there are two ways to measure instance of autism — density and cumulative instance, since it is difficult to pinpoint the onset of the disease. By using a 7-year cumulative diagnosis, it is then possible to make a solid diagnosis of autism, and the data can be compared with CDC data, which is measured at the age of 8. Also, Korean children enter school at 7, and the response rate for screening at that age is very high. As to Dr. Cordero's second question, Dr. Kim said that determining mechanism is quite complicated, with many factors influencing epigenetic modifications.

Dr. Birnbaum noted that many children on the spectrum have GI problems. She asked whether Dr. Kim had plans to gather fecal samples to look at microbiome issues. Dr. Kim said she would like to do so, but the children in her cohort are too old, with their microbiomes being results of their symptoms rather than a cause. She said that in another, younger cohort she has, she would like to collect biosamples and placental samples from pregnancy through age two to address the question.

Dr. Manautou noted that in her study Dr. Kim had seen a considerable number of people with psychiatric disorders among the parents who smoke. He asked whether the data was robust enough to segregate people with psychiatric disorders to determine whether a subset may show increased risk for children with ASD. Dr. Kim said they had tried to do so, but the number of subjects was too small, and there is still much stigma related to psychiatric disorders in Korea, so underreporting was likely a factor.

Dr. Coronado asked whether Dr. Kim was finding ASDs to be more common in siblings. Dr. Kim noted that the statistical approach in her study required only children to document *de novo* mutations.

VII. Concept Clearance Proposal: Population-Based Model Organism Research for GxE Exploration in Complex Disease Outcomes

Dr. Kim McAllister presented the concept clearance proposal on population-based model organism research to Council

In recent years, heterogeneous strains of mice have been developed to better predict responses in a heterogeneous human population. They include the Collaborative Cross (CC) and Diversity Outbred (DO) mice. A 2015 meeting at NIEHS explored how those resources could be used in the environmental health sciences community. The main recommendation that emerged from the conference was that there was a need for additional proof-of-principle studies to catalyze the use of population-based rodent resources to toxicology and environmental health sciences. There remains an impression that the population-based rodent resources are under-utilized in the environmental health sciences community, due to lack of recognition or awareness, issues associated with NIH study section review, and money, since larger budgets are sometimes necessary to cover the costs of breeding and maintaining the mice.

The overall goal of the proposed RFA is to stimulate the use of population-based model organism resources for environmental health science questions relevant to human disease outcomes, to allow the resources to become more firmly established as mainstream in the field. It would fund proof-of-principle studies needed to accelerate the impact of the emerging field. The FOA will be reviewed by a Specialized Emphasis Panel convened by the NIEHS Scientific Review Branch. NIDA, NIAID, and NCI have expressed possible interest in becoming involved in the initiative. It would incorporate the requirement of a strong data management and sharing plan.

According to Dr. McAllister, "These unique resources have the potential to be powerful tools for generating hypotheses related to gene-environment interplay in human disease, performing controlled exposure studies to understand the differential responses in humans for susceptibility or resistance to environmental exposures, and identifying gene variants that influence sensitivity to toxicity and disease states."

Dr. Feinberg was the first Council reviewer. He noted that the proposal addresses two of the Institute's strategic priorities. He discussed some of the technical advantages offered by the DO and the CC, but noted that he did not see a significant advantage with the DO. He said that the 2015 meeting did not discuss epigenetics, and that it is important to include that discussion in this initiative. "The epigenetic information obtained in these studies might be more directly portable to human environmental health studies, because the actual genotypes with regard to the mice might not exactly be clear how that's related to human," he observed. He felt that the funding for the project might be too modest. He approved of the idea of leveraging the interest of the other institutes, as it "seems like a fertile area for inter-institute collaboration." Overall, he felt that the concept was well supported by the "outstanding workshop" and the provided documentation.

Dr. Eaton said that from a mechanistic perspective, the proposal is a good one, but from a more classical toxicology perspective, it is more challenging when trying to make an association between exposure and outcome. He cited the possibility of false positives and false negatives in the diverse population, but noted, "I think that the outbred strains and this whole approach is really valuable from a toxicological perspective." The statistics would be the biggest challenge, he observed. He agreed that the budget is probably too small. He said an R21 approach would probably not be useful. Overall, he said, it is a good opportunity.

Dr. Manautou agreed that an R21 mechanism would be the way to go in this instance.

Dr. Feinberg recommended that strong attention be paid to statistical methodology in the RFA.

Dr. McAllister mentioned that one of the concepts to emerge from the 2015 workshop was that there would be some scenarios that would not be appropriate for the CC and the DO, but there are many types of studies in which those animal models would be useful.

Dr. Ho noted that breeding and maintenance of the CC and DO populations must be done carefully to maintain diversity. She also discussed the importance of the toxicant being studied to have a very clear threshold or dose response curve. Otherwise, the experiment would be too expensive.

Dr. Zeise mentioned a recent NAS report on incorporating newer, emerging science in risk assessment, which included a strong call for increased use of the CC and the DO. She discussed the importance of study design for project using the models, and added, "I think there's a lot of enthusiasm by risk assessors for incorporating and doing a lot more with these models."

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

VIII. FOA: Extending Genome Integrity Assays to Population Studies

Dr. Les Reinlib presented the concept to the council. He noted that genome integrity research is a cornerstone of environmental health sciences research, because a variety of different chemicals and stressors directly affect DNA, which can predispose an individual to a disease. He described a select set of recent clinical and population studies that invoke the recognition that insights on genomic integrity pathways can inform measures of disease risk as well as treatment protocols. However, there are several factors limiting the use of genome integrity assays in population studies, leading to a discernible gap in knowledge. Dr. Reinlib described several of the newer technologies available to assay DNA damage or repair. He went over the June 2015 workshop devoted to the topic, which led to recommendations that inspired the program concept.

The highly technological program would provide funds for basic scientists and epidemiologists to work together to improve existing assays and approaches in order to produce practical tools to meet the needs of epidemiological studies. Five or six projects would be funded at a total of $3.5 million per year under a U01 cooperative agreement. $800,000 in opportunity funds would be added in year 3. Dr. Reinlib noted that NCI and the NIA are potential federal partners who may be interested in participating.

Dr. Ahsan was the first Council discussant. He said the project is timely and that it is now feasible to consider including the assays in large population studies. He approved of the idea of using a centralized assay facility. He said that the only limitation is the current focus on polymorphisms in lymphocytic DNA. However, genetics remains the major determinant of phenotype, so it may be worth considering keeping that component along with the other elements of the program. Dr. Reinlib replied that the program expects to continue to foster gene-environment studies. He noted that some of the existing population studies do take those polymorphisms into account as they impact repair capacity, so it makes sense to incorporate that type of data.

Dr. Kaminski was the second Council discussant. He noted that the RFA is focused on developing and advancing technology, which needs to be strengthened and improved in this area. He approved of the U01 cooperative agreement mechanism to be employed. He said that the temptation will be to use leukocytes because they are easy to obtain, but clearly tissues beyond blood cells should be sought. He supported the idea of biologists and epidemiologists working together. He said he was very supportive of the concept. Dr. Reinlib said the proposal had been in the works for many years, and now the appropriate proofs of concepts have come to fruition to ensure success.

Dr. Sung said it was important to mix the biologists and epidemiologists. He noted that R01 scientists tend to be secretive, which is a different dynamic than the proposed project. He said he was surprised such a project had not already been done. He asked what was meant by "improved interpretation of results." Dr. Reinlib replied that among the current problem is the lack of standardization of the assays. He said that improved assays would yield improved prediction of disease as well as improved confidence in the polymorphisms involved.

Dr. Ho said that it was important that single-cell technology be part of the project. She added that with some of the assays, the percentage of cells available is most important, which may become a limitation with the cooperative nature of the project.

Dr. Winn said that NCI is already very interested in the project. She asked for more information about the metrics involved. She asked about the tipping point for deciding to scale up a particular assay to the population level. Dr. Reinlib replied that once an association between individual pathways of genome integrity and susceptibility, the field "will really start to take off" and become a mainstay of the research. He noted that although this initiative is designed to be technological, the hope is that new biomarkers will be discovered.

Dr. Collman asked for and received a motion and second to approve the concept clearance. The Council voted unanimously in favor of the concept.

IX. Molecular Mechanisms of Protein-DNA Crosslink Reversal

NIEHS Scientific Director Dr. Darryl Zeldin introduced Dr. Scott Williams, senior investigator and deputy chief of the Genome Integrity and Structural Biology Laboratory, who briefed the Council on recent work emerging from his laboratory.

Throughout his career, Dr. Williams has spearheaded efforts to define mechanisms of action of important DNA damage response factors that dictate cellular response to DNA strand breaks. He described his lab's work looking at one of the specific factors and a specific pathway for the resolution of an important form of protein-DNA crosslinks, the topoisomerase-DNA cleavage complex. He noted that cellular topoisomerases are present in all kingdoms of life, serving to resolve DNA entanglement. Some of the most potent antibiotics and chemotherapy agents act by blocking the TOP2 enzyme in mammalian cells. The TOP2 DNA topoisomerases act to resolve DNA topology through an elegant, but very complicated reaction. However, they pose unique threats to genomic integrity. Pre-existing DNA damage, environmental toxicants, and chemotherapeutic drugs poison the enzymes, generating highly genotoxic DNA double-strand breaks. Dr. Williams and his colleagues have been studying the cellular TOP2 DNA damage clearance apparatus. Their work establishes a novel paradigm for the direct resolution of TOP2-DNA protein crosslinks by the tyrosyl-DNA phosphodiesterase complex, with implications for cancer therapy chemoresistance.

Dr. Sung asked Dr. Williams about the use of zinc fingers. Dr. Williams explained that it was thought that the zinc fingers are involved in topoisomerase binding.

X. Open Council Discussion

Dr. Collman began the discussion period by describing outreach from the NCI soliciting more involvement in the Cancer Moonshot program. Dr. Birnbaum had responded, suggesting that NIEHS become involved with the working group related to cancer prevention and early detection strategies. Dr. Collman presented the recommendation and implementation plan from the Precision Prevention and Early Detection Working Group. She asked Council to discuss how NIEHS would best be involved in the implementation committee, of which she and Dr. Bucher were now members. The implementation group is currently working on initiatives to recommend for using 2018 funding.

Dr. Bucher described NTP's involvement with the UK initiative aimed at sequencing 5,000 tumors. NTP will be providing archival tissue to the effort.

Within the Moonshot's rubric of early detection, Dr. Eaton asked Dr. Bucher how many compounds in the NTP's experience have tested positive, with a fairly strong response, to look at early changes in animals that are known to go on to develop cancers in the target tissues. Dr. Bucher replied that most of the studies have been pre-chronic studies, conducted along with the 2-year studies. Dr. Collman noted that it may be an opportunity to share some NTP resources with the wider cancer research community. Dr. Eaton pointed out that the advantage of doing so would be knowing which target tissues to look at, thanks to the outcomes of the longer-term studies. Dr. Bucher mentioned that NTP has fewer frozen tissues than paraffin-embedded, formalin-fixed samples.

Dr. Ho speculated that NIEHS, by concentrating on sequencing tumors to contribute to prevention knowledge, is "missing half the picture." Given that it takes many years for cancer to develop, it would be useful to sequence tissue before cancer occurs, even cancer cells floating freely around the body. She noted that The Cancer Genome database lacks data on normal tissues. Dr. Bucher said that there is a plan to do normal tissue or at least adjacent tissue as well. Dr. Ho emphasized that it is important to collect cancer cells 1-5 years prior to the development of the disease, possibly yielding much earlier biomarkers.

Dr. Litchveld said there is an opportunity to do earlier bio-banking, to look more closely at what works in cancer prevention. She noted that the Moonshot plan shown by Dr. Collman did not include examination of the role of culture in cancer prevention. She noted the need to link what is happening in the lab to what is going on in high-risk populations — not only looking at people who already have the disease, but looking much further upstream.

Dr. Miranda addressed option #9 in the implementation plan ("Develop best practices to ensure participation across populations). She noted the large amount of work on community engagement connected to the Center programs. In the case of NIEHS, there is a geography involved due to the effort to identify populations affected by particular exposures. She said NIEHS has a particular expertise in engendering trust in communities to bring high-risk individuals into research.

Dr. Feinberg noted that the story of p53 was originally an environmental health story. He said he was concerned about efforts to link sequence data with exposures. He felt that there is still an opportunity to couple cancer prevention strategies and samplings taken to assess cancer risk.

Dr. Brown said there are cohorts in existence that would be ideal to look at. He cited several examples.

Dr. Winn noted that one of the Moonshot's goals is to accelerate the science, "to do things in five years that should have taken ten." She mentioned that there is a Participant Engagement Network, which is one of the main themes in the Blue Ribbon Panel report. She said that although it is not specifically named as a main theme, the issue of health disparities will certainly be included.

Dr. Collman noted that one of the Blue Ribbon Panel's recommendations was to "expand use of proven cancer prevention and early detection strategies." She said that suggests that the effort is not to discover new methods, but to take those that all agree are the best strategies and amplify them to offer new opportunities. She also noted the panel's recommendation that the effort focus in the highest risk individuals. She described the NIEHS/NTP approach to risk, which includes such factors as exposures, geography, and environmental justice. She said that she hopes that she and Dr. Bucher can help expand the committee's thinking so that environmental health science issues can become part of the dialogue.

Dr. Birnbaum said that she was pleased with the opportunity to enlighten colleagues about the role of the environment in cancer and the importance of prevention.

Ms. Waghiyi described the situation on her native St. Lawrence Island in Alaska, which has suffered considerable environmental contamination. She discussed the important elements of researchers working together effectively with communities, such as involving community members from the beginning of a project, treating community members as peers, and working with key people to develop trust.

Dr. Coronado described a cancer cluster in her Texas-Mexico border area. She asked for clarification on #8 on the implementation plan list ("Extend success to somatic cancers in the general population"). Dr. Birnbaum speculated that it addresses the fact that so much focus is currently looking at germline mutations and heterozygous characters, which can lead to assessing somatic mutations.

Dr. Ahsan said that he sees a lot of potential energy that could be exploited with some planning. Dr. Winn said that it will be important to leverage the activities of the Moonshot, relying on what has been learned by previous efforts, and ensuring that there is not duplication of efforts.

Dr. Lichtveld stressed that "It's about people." She said she was pleased that community engagement research would potentially accelerate over the next five years. She urged that community engagement not be limited to simple participation, and that it be recognized that community members can be equal and important partners in the research enterprise. Dr. Birnbaum agreed, and said that that is what NIEHS is all about, with this project being an opportunity to help other NIH agencies, particularly NCI, appreciate its approach.

Dr. Elliott noted that the "highest risk individuals" in the Moonshot Blue Ribbon Panel recommendation probably referred to high risk from a genetic mutation standpoint, and it would be good to get the thinking to include high risk from an exposure standpoint. Citing #9 on the implementation plan list (Develop best practices to ensure participation across populations), he said he would like to see research on how people in high exposure communities can be empowered to change their exposures. Dr. Collman said it should not be difficult to communicate that message, particularly given NIEHS's experience in that area. Dr. Elliott added that it would be good to use many examples of social science type efforts to empower communities.

Dr. Kaminski said that one element NIEHS can bring to the table as its unique niche is to describe the environmental factors of concern. Exposure is another area in need of improvement, as well as identifying the biomarkers that should be focused on as cancer signals.

Dr. Ho noted that cancer prevention should be considered using a life course approach, understanding that known windows of vulnerability should be looked at as opportunities for prevention. She said that immigrant populations should be considered to be vulnerable, as research has shown that immigrants suffer increased cancer when they move to more cancer-prone areas.

Dr. Cordero wondered whether children would be included. Dr. Collman said they would be. Dr. Ho added that children are important, as those with cancer are surviving at much higher rates.

Dr. Birnbaum noted that the All of Us cohort would not recruit children at the beginning of its program, but would eventually have families, including parents and children. She mentioned the ECHO program, with 35 grantees and more than 80 cohorts, offering opportunities to conduct various follow-ups. She stressed that there is nothing in the Moonshot program to exclude children. She said that aspect should be championed, because "it may be something that we can push on, because what happens early on is going to impact the rest of the life."

Dr. Collman concluded the discussion, thanking the Council members for their input, and encouraging them to send more ideas as they might have them.

XI. Report of the Director, DERT

Dr. Collman updated the Council on developments in the Division of Extramural Training and Research (DERT) since the September, 2016 Council meeting.

She welcomed several new DERT staff members.

She noted the January 1, 2017 NIH implementation of the Final-Research Performance Progress Report, which replaced the Final Progress Report for project closeout, and the new requirement for an Interim-RPPR (Research Performance Progress Report) while grant renewal applications are under consideration. She mentioned the availability of new CSR webinars to help navigate peer review.

She presented the 11 Council Delegated Staff Actions, none of which changed since 2016. She asked for and received a motion to approve the measure. Council voted unanimously in favor.

She recounted several new funding opportunities and an upcoming meeting at NIEHS on Environmental Risks for Psychiatric Disorders. She updated Council on developments with the Epidemiology Resources Catalog, which she had introduced to the panel in 2015. She described a new feature on the Superfund Research Program website, with access to datasets from individual SRP Centers. Datasets are also available at the subproject level.

Continuing the theme of “big data,” Dr. Collman described the requirements for NIH funded researchers to access CHEAR (Children’s Health Exposure Analysis Resource). She also related how to apply to CHEAR, and the review cycle.

She provided a wrap-up of the FY 2016 budget. For NIEHS, the key points were:

- Of 255 competing awards made, 164 were RPGs, 23 were SBIR/STTRs, 23 were training, and 5 were Centers. 1,627 applications were received.
- Total RPG funding was $234 million; the average cost of an RPG was $387,000.
- Total R01 funding was $172 million; the average cost of an R01 was $451,000.
- Success rate was 14.2% for all RPGs and 15.2% for R01s.
- Payline was at the 10 percentile for R01, R03, and R21 grants.

She provided several more details and data regarding FY2016 budget parameters. She described several new initiatives planned for FY2017, including set-aside funding totaling $33,850,000.

Dr. Collman discussed the funding philosophies and challenges related to DERT funding decision-making. Given current budgetary uncertainties, she emphasized that the focus will remain on funding the highest possible scientific quality. She concluded her presentation by going over current practices in funding decisions, and asking Council to consider several questions related to funding decision-making.

Dr. Guilarte asked about the fate of the R35 mechanism. Dr. Collman said it would be coming to May 2017 Council for consideration, as it is currently under review. Dr. Guilarte said that budget cuts during the third or fourth year of an R01 did not allow researchers to finish their experiments, creating many issues. Dr. Collman said that investigators know what their funding will be over the entire course of the grant. In rare circumstances, there is consideration given to cutting the Type 5 or out years.

Dr. Manautou asked for more information about the R56 mechanism. Dr. Collman explained the mechanism, which provides short-term funding for grants outside the payline.

Dr. Cordero asked about a comparison between NIH and NIEHS in terms of geographic areas covered in terms of academic institutions. Dr. Collman said that the full portfolio covers most of the country. When making funding decisions, geographic distribution is not the focus, but we are cognizant of it.

Dr. Eaton asked about the difference in success rates between Type 1 and Type 2 grants. Dr. Collman said she did not currently have that information, but would pursue the question.

Dr. Miranda said she objected to NIH use of the term, "non-competing," and suggested changing it to "continuing" or "ongoing." Dr. Birnbaum agreed.

XII. Sharing the NIEHS Story – A 2016 Review

Ms. Christine Bruske Flowers, director of the NIEHS Office of Communications and Public Liaison, gave the Council a report about a very busy year for the communications team – 2016. She went over several highlights, including media relations with regard to the NTP Cell Phone Study and the NTP 14th Report on Carcinogens. She summarized a variety of website developments and social media initiatives. She related a list of many communications accomplishments associated with the NIEHS 50th anniversary celebration – a yearlong program of events.

Overall, in 2016, NIEHS and NTP scientists gave 214 media interviews, 34 of which were done by Dr. Birnbaum. NIEHS grantees made 681 tweets during the year.

The 50th anniversary celebration comprised a total of 44 events, starting with a kick-off and homecoming for retirees in January, and culminating in a special celebration November 1, the actual 50th anniversary, which featured several distinguished speakers. The Environmental Health Science FEST, held December 4-8 in downtown Durham, was a great success. Finally, on December 13, the 50th anniversary time capsule was sealed, creating a permanent collection of NIEHS historical items and scientific artifacts.

Ms. Flowers also distributed to Council members the NIEHS history and milestone booklet, "Celebrating 50 Years of Environmental Health Research at NIEHS," and shared an 8-minute history video produced for the celebration.

Dr. Coronado asked Ms. Flowers about collaboration with teachers. Ms. Flowers said that the next speaker, Dr. Ericka Reid, would provide details about that type of interaction. Dr. Coronado asked if there were links with minority language media. Ms. Flowers replied that many materials are translated into Spanish, and even Vietnamese in the case of the Gulf Study. She said NIEHS gets much interest from throughout the world, with many web visits coming from other nations.

Dr. Brown asked if there was any specific outreach to the Society of Environmental Journalists. Ms. Flowers replied that there is a strong relationship with that organization and NIEHS is very active.

XIII. The Office of Science Education & Diversity...where outreach forwards access and opportunity!

Dr. Ericka Reid, Director of the NIEHS Office of Science Education & Diversity (OSED) provided Council an overview of the office and an update on its activities.

She related the history of OSED, and described where it fits in the current NIEHS Strategic Plan. She also read the group's mission and vision statements, and recognized its current staff. She provided details about OSED's many activities related to its three focus areas: K-12+ science education, community engagement and outreach, and diversity initiatives. Among the diversity initiatives, OSED organizes the NIEHS Scholars Connect Program, which is a paid 3-semester research training internship connecting local STEM-focused undergraduate students with environmental health science. Since the program's inception in 2012, 28 scholars have been admitted. Seven have gone on to graduate studies.

OSED also oversees the Environmental Health Science Education website, organizes NIEHS campus tours, and manages the NIEHS Speakers Bureau.

Dr. Brown commented that he had no idea of the extent of the work conducted by OSED as described by Dr. Reid. He was particularly interested in the Citizen Schools program, and recommended outreach to investigators about the initiative.

Dr. Eaton recalled a letter he had written to NIEHS leadership in 1991 recommending that the institute develop educational materials for high school students, with a response that it was not really part of the NIEHS mission. He was pleased to see how much things had changed over the years since. Dr. Birnbaum observed that there are still challenges related to K-12 work, including a ban on STEM education by NIH recently proposed in Congress. The issue was that STEM education should be conducted by the National Science Foundation, not NIH.

Dr. Litchveld informed Dr. Reid that "I am on your bandwagon." She asked whether the Scholars Connect program was only for local area students. Dr. Reid replied that it is, because it is an academic year program. Dr. Litchveld described a similar program at her institution that includes a teachers' component and a junior high school component. Some of the funds are also used to supply labs in local high schools. She asked whether her teachers would be eligible for the teacher workshops conducted by NIEHS. Dr. Reid said the workshops are not just for North Carolina science teachers. Dr. Birnbaum described the genesis of the Scholars Connect program, and termed it "a nice success."

Dr. Manautou asked about the STaRS (Science, Teachers and Research Summer Experience) program mentioned by Dr. Reid, inquiring about what the follow-up is, and how its impact is assessed. Dr. Reid said that was to be phase II of the evaluation plan.

Dr. Elliott discussed Dr. Reid's allusion to Goal 9 of the NIEHS Strategic Plan, which addresses training and diversity, as well as interdisciplinary diversity. He asked whether there was a connection to the group at NCI working on team science. Dr. Collman said that NIEHS is very aware of their work, and may be pursuing such a connection. Dr. Winn said that the group's materials are widely available, and praised NIEHS's efforts in encouraging transdisciplinary work.

XIV. CounterACT Update

Dr. Sri Nadadur updated Council on the CounterACT (NIH Countermeasures Against Chemical Threats) Program, which is a congressionally mandated trans-NIH program, in which NIEHS has been actively involved since its inception more than a decade ago.

He summarized the program's goals, organization, and mission. The program includes a comprehensive network of Research Centers of Excellence, individual research projects, SBIRs, contracts, and interagency agreements with the Department of Defense. The success of the program's efforts is measured by transition of lead compounds to advanced development efforts supported by the Biomedical Advanced Research & Development Authority (BARDA).

Dr. Nadadur described the CounterACT research portfolio, much of which centers on developing medical countermeasures for the effects of exposure of a wide range of pulmonary threat agents such as chlorine and sulfur mustard. Research also includes a functional genomics approach for targeting medical countermeasures for multiple toxicants. He said that two medical countermeasures, one each for chlorine and sulfur mustard, have transitioned to BARDA, while four others (two for chlorine, one for acrolein and one for sulfur mustard skin lesions) are in the process of transition to BARDA. The portfolio is being expanded to look at other threat agents.

The 10th annual NIH CounterACT Network Research Symposium will be held June 12-14 in Boston.

Dr. Birnbaum asked Dr. Nadadur why ammonia is not one of the threat agents being addressed by CounterACT. Dr. Nadadur replied, currently we do not have any grant application on this.

Dr. Coronado asked whether the program receives any funding from the Department of Defense (DoD) or the Department of Homeland Security. Dr. Nadadur replied that the NIH CounterACT program, through an IAA, supports research efforts at US Army's Medical Research Institute of Chemical defense and there are interactions between the two programs, but DoD does not provide separate funding to CounterACT.

XV. TaRGET II Update

Dr. Fred Tyson updated the Council on the second phase of the program called TaRGET — Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription. TaRGET is a multi-phased program with four components, and was initially presented to the May 2012 Council for concept clearance. The overall objective of the program is to enhance understanding of how exposures perturb epigenomes, epigenetic processes, and biological pathways to influence disease pathogenesis.

TaRGET II, in progress from 2016-2021, focuses on identifying epigenomic signatures in mouse tissues exposed to environmental challenges and asking if the changes observed in target tissues are conserved or correlative in surrogate tissues. This is being done strictly in mouse models, and is meant to inform how similar studies in humans can be conducted. The TaRGET II consortium objectives are:

- Production of exposure-induced epigenomic signatures
- Correlative analyses of target and surrogate signatures
- Correlation of epigenomic changes and phenotype
- Persistence across the lifecourse
- Windows of susceptibility
- Genetic context

Dr. Tyson went over the programs U01 awards, and described its Data Coordinating Center, including its year one milestones. He discussed the individual projects of the consortium research teams, from North Carolina, the University of Michigan, Baylor and the University of Pennsylvania, the University of Chicago, and Johns Hopkins and Case Western Reserve. There is also an External Science Panel to recommend approaches and assess priorities.

Dr. Guilarte said that TaRGET II is an important undertaking. He asked Dr. Tyson what was meant by "frontal cortex neurons," given that there are many more glial cells than neurons in the frontal cortex. Dr. Tyson noted that the investigator, Dr. Dolinoy from the University of Michigan, has been working with colleagues from North Carolina State University to develop protocols for extracting neurons. Dr. Guilarte observed that even if an *in vitro* system is used, there must be glial cells, because the neurons would not survive.

Dr. Kaminski agreed that the ability to compare changes in blood cells to changes in tissue is the strength of the approach, and that it will yield important information. He asked how the data from these primarily mouse studies would be related to humans. Dr. Tyson said that the program is looking at whole blood, because that is the main focus of current population-based studies. In terms of looking at upstream elements, there are some limited assays such as histone modification analysis, but such tests are costly. Dr. Kaminski clarified that he was focusing on how genes are regulated across species, where the overlap between species in terms of regulatory genes is often small. He wondered how the information on gene regulation in the mouse would be extrapolated to humans. Dr. Tyson said that direct comparisons would not be conducted, but the effort is to try to find out under what kind of conditions the surrogate analyses can be conducted and can be expected to yield meaningful.

Dr. Feinberg noted that the pursuit is limited by looking at a restricted genome. He recommended that the issue be explored with the advisory panel.

Dr. Miranda said that Dr. Dolinoy, who was listening to the meeting, had texted her an answer to Dr. Guilarte's question. She said the team is now using a new technology that will do single-cell transcriptomics on all cells. They will not ignore glial cells in their work.

XVI. Adjournment

Dr. Birnbaum thanked the presenters, the Council members, and the staff for their participation in the meeting. She said it was great to hear about so many exciting NIEHS/NTP programs. Dr. Collman added her thanks to everyone.

The meeting was adjourned at 11:30 a.m., February 15, 2017.

CERTIFICATION:

Linda S. Birnbaum

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

Gwen W. Collman -S

Digitally signed by Gwen W. Collman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=0010046637, cn=Gwen W. Collman -S
Date: 2017.03.30 22:09:56 -04'00'

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

Attachment:
Council Roster