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

MEETING SUMMARY OF THE NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL

February 12-13, 2024

The 171st meeting of the National Advisory Environmental Health Sciences Council convened on February 12 and 13, 2024. Open session convened at 9:03 am and ended at 3:45 pm February 12. A closed session took place from 4:00 pm to 5:00 pm February 12. Open session began at 9:02 am and adjourned at 12:36 pm on February 13. Dr. Rick Woychik, Director, NIEHS, presided as chair. The meeting was virtual; all participants attended via Zoom.

Participating Council Members

Yulia Iossifova Carroll, MD, PhD (*ex officio*)
Stephania Cormier, PhD (*ad hoc*)
Olivier Deschenes, PhD (*ad hoc*)
Suzanne Fitzpatrick, PhD (*ex officio*)
Andrew Geller, PhD (*ex officio*)
J. Timothy Greenamyre, MD, PhD
Irva Hertz-Picciotto, PhD
Andrij Holian, PhD
Darryl Hood, PhD
Keri Hornbuckle, PhD
Cathrine Hoyo, PhD (*ad hoc*)
Jani Ingram, PhD
Andrew Jorgenson, PhD
Gary Miller, PhD
Gökhan Mutlu, MD
Patricia Nez Henderson, MD
Trevor Penning, PhD
Maria Savasta-Kennedy, JD
Karen Vasquez, PhD

NIEHS Staff

Kathy Ahlmark
Trevor Archer, PhD
David Balshaw, PhD
Jennifer Baker
Linda Bass, PhD

Kris Battle
Sharon Beard
Abee Boyles, PhD
Michelle Campbell
Danielle Carlin, PhD
Toccara Chamberlain
Jennifer Collins
Gwen Collman, PhD
Yuxia Cui, PhD
Christie Drew, PhD
Beverly Duncan, PhD
Chris Duncan, PhD
Anika Dzierlenga, PhD
Maya Evanitsky, PhD
Christine Flowers
Murali Ganesan, PhD
Amanda Garton
Julia Gray
Kimberly Gray, PhD
Jenny Greer
Arshya Gurbani
Janet Hall, MD, MS
Astrid Haugen
Patricia Henderson, PhD
Heather Henry, PhD
Jon Hollander, PhD
Mike Humble, PhD
Gary Johnson
Bonnie Joubert, PhD
Alfonso Latoni, PhD
Cindy Lawler, PhD
Gerald Lilly, MD, MPH
Mbeja Lomotey, Dr.P.H.
Lindsey Martin, PhD
John Maruca
Jacqui Marzec
J'Ingrid Mathis
Kimberly McAllister, PhD
Elizabeth McNair
Latavia Miller
Parris Milly
Nathan Mitchiner
Srikanth Nadadur, PhD
Liam O'Fallon
Suzy Osborne
Eric Persaud, DrPH

Kristi Pettibone, PhD
Nicole Popovich
Ashlinn Quinn, PhD
Jim Remington
Francoise Santos
Chris Schnur
Thaddeus Schug, PhD
Dan Shaughnessy, PhD
Carol Shreffler, PhD
Varsha Shukla, PhD
Robert Sills, PhD
Cyrena Silvera
Claudia Thompson, PhD
Brittany Trottier
Tierra Tucker
Fred Tyson, PhD
Ashley Vargas, PhD
Leroy Worth, PhD
Rick Woychik, PhD
Darryl Zeldin, MD
Shanshan Zhao, PhD
Alicia Zorn

Members of the Public Present

Thomas Begley, PhD, SUNY-Albany
Justin Colacino, PhD, University of Michigan School of Public Health
Victor Corces, PhD, Emory University
Stephania Cormier, PhD, LSU
Yvonne Fondufe-Mittendorf, PhD, Van Andel Institute
Ernie Hood, Bridport Services, LLC
Ting Wang, PhD, Washington University in St. Louis
Yunsun Nam, PhD, UT Southwestern
Yinsheng Wang, PhD, University of California, Riverside

OPEN SESSION

The meeting was open to the public on February 12, 2024 from 9:03 a.m. to 3:45 p.m. and on February 13, 2024 from 9:02 a.m. to 12:36 p.m. In accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), the meeting was closed to the public on February 12, 2024 from 4:00 p.m. to 5:00 p.m. for consideration of grant applications. Notice of the meeting was published in the *Federal Register*. Dr. Rick Woychik presided as Chair.

I. Call To Order and Opening Remarks, Review of Confidentiality and Conflict of Interest

NIEHS and NTP Director Rick Woychik, Ph.D., welcomed attendees and called the meeting to order. He read the Government in the Sunshine Act. DERT Director David Balshaw, Ph.D., asked Council members in the room and present on the Zoom call to introduce themselves. Members of the NIEHS senior leadership team introduced themselves. Dr. Balshaw went over some of the logistics for the meeting, and read the conflict of interest statement. Council member Philip Bourne, Ph.D., was unable to attend.

II. Consideration of September 2023 Meeting Minutes

Approval of the September 2023 meeting minutes was moved by Dr. Savasta-Kennedy and seconded by Dr. Miller. Council voted to approve the minutes, with all in favor.

III. Empowering Environmental Research through Novel Statistical Methods

NIEHS Scientific Director Dr. Darryl Zeldin introduced Dr. Shanshan Zhao from the Applied Statistics Group. Dr. Zeldin said that the overarching goal of Dr. Zhao's research program is to develop powerful statistical methods to discover how human interactions with the environment influence health and well-being.

Dr. Zhao highlighted the NIEHS Sister Study and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, which are both large-scale, population-based studies. Her work concentrates on assessing disease risk in space and time, looking at the spatial and temporal patterns of breast cancer risk and what environmental exposures are related to observed patterns. She provided details about the Sister Study, and described several publications that have emerged from it using advanced statistical methods. Studies have elucidated the spatial distribution of breast cancer risk, including consideration of a list of several environmental exposures that may contribute to breast cancer risk. Analysis has shown that the exposures explained 21.4% of the spatial variation in overall breast cancer incidence, and 63.3% of the spatial variation in ER+ breast cancer incidence.

She discussed statistical analysis of SEER Louisiana breast cancer mortality data, and showed how spatial location was an important factor, as well as the impact of several other elements such as access to care, quality of care, and socioeconomic status. The data also showed the trends in breast cancer incidence rates over time, including a longer survival time (data from 2000-2013) and the impact of notable events such as

Hurricane Katrina and passage of the Affordable Care Act. Katrina was the most significant event, with an impact that lagged by 14 months and lasted for 2 years and 7 months.

Dr. Zhao also described her group's work developing new statistical methods related to environmental mixtures analysis. She noted that in many environmental studies, chemical measures are subject to limit of detection (LOD). The study she reported on involved the LIFECODES cohort, women in the Boston area who planned to deliver at Brigham and Women's Hospital between 2006 and 2008, looking at the relationship between 17 urinary trace metals and the oxidate stress biomarker 8-isoprostane. The group developed an innovative statistical approach involving a two-stage method, which largely overcame the LOD issue.

Dr. Hertz-Picciotto asked Dr. Zhao if she had any data on earlier life exposures or location changes. Dr. Zhao said that her group was interested in looking at those questions, particularly the impact of childhood residential addresses.

Dr. Zeldin asked about the generalizability of the spatial and temporal models the group has developed and how they may apply to other diseases or other cancers. Dr. Zhao said they are using SEER data to look at mortality and incidence trends in colorectal cancer, as well as different age groups.

Dr. Hood asked about what her advances might mean for some of the other gynecological cancers. Dr. Zhao said they have not looked at them yet, but they are open to other ideas or suggestions.

Regarding the Louisiana data, Dr. Geller noted that it covered several industries, and asked if it also included the chemical industry, which is quite prevalent in the state. Dr. Zhao said they had not specifically looked into that, but had relied on data that had more general clustering of industries. She added that she would love to include that type of information into the secondary analysis.

IV. NIEHS-supported Environmental Epigenomics & Epitranscriptomics

Dr. Balshaw then introduced the next series of presentations, a mini-symposium on epigenomics and epitranscriptomics, and the crosstalk between nucleic acid modifications. NIEHS Deputy Director Trevor Archer, Ph.D., moderated the session. Dr. Archer introduced Dr. Fred Tyson for the initial presentation to set the stage for the mini-symposium.

He provided an overview of how NIEHS supports this aspect of the research portfolio as it develops and continues to evolve. He briefly reviewed the central dogma as DNA is transcribed into RNA, which is then translated into proteins. The process is far more

complicated than that simple linear concept. Epigenomics is a process of turning on or off gene transcription with reversible chemical modifications. Epitranscriptomics is a process associated with the study of reversible modification of transcripts or nucleosides, with the caveat that the RNA alphabet building blocks are not restricted to the four canonical bases. A number of different modifications can be added to transcripts. As with epigenomics, they are installed and recognized by readers, writers, and erasers (proteins). The chemical modifications alter the structure and function of RNA. All RNA species studied thus far are modified. There are currently 300 known modifications.

Dr. Tyson reviewed the development of the NIEHS environmental epigenomics portfolio, stemming from a series of workshops and RFAs spanning two decades. The investment has been fruitful, reflected by the increasing number of manuscripts published each year on environmental epigenomics citing NIEHS as a source of funding. The Roadmap Epigenomics Program had as its centerpiece the Reference Epigenome Mapping Consortium (REMC), which had several notable achievements. It also gave rise to the formation of the International Human Epigenome Consortium (IHEC), which has set many of the data standards and metrics the field now uses. To add an environmental exposures aspect, NIEHS developed the TaRGET program (Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription). TaRGET I sought to elucidate how epigenetic modulators and processes respond to the environment and enhance our understanding of how environmental exposures perturb the epigenome. The Target II program established a research consortium to use mouse models of disease-relevant environmental exposures to generate specific epigenomic signatures in tissues associated with pathologies such as metabolic or neurodevelopmental disorders, and to identify correlative signatures in surrogate tissues that are less invasively obtained. The third goal was to develop a community data resource. Both programs have regularly published in high-impact journals.

Dr. Tyson also discussed the NIEHS epitranscriptomics portfolio. He described two groundbreaking studies that revolutionized the field. Recognizing the potential impact of environmental toxicants on the deposition, removal, and recognition of RNA modifications and how it might be mechanistically associated with a number of different health outcomes, NIEHS embarked on developing a portfolio that would include exposures in epitranscriptomics research. There are currently over 35 active grants in the area, with considerable productivity and many publications in high-impact journals.

Going forward, there will be continued research on crosstalks between the epigenome and the epitranscriptome, as mounting evidence is pointing to. It is anticipated that the portfolios will contribute in many ways to Precision Environmental Health and Exposomics initiatives.

Dr. Tyson concluded by introducing the roster of speakers for the mini-symposium:

- Yinsheng Wang, Ph.D., University of California, Riverside
- Yvonne Fondufe-Mittendorf, Ph.D., Van Andel Institute
- Justin Colacino, Ph.D., University of Michigan
- Victor Corces, Ph.D., Emory University
- Tom Begley, Ph.D., SUNY-Albany
- Yunsun Nam, Ph.D., UT Southwestern
- Ting Wang, Ph.D., Washington University in St. Louis

V. Multi-omics Approaches in EHS—RNA Adenine Methylation in CAG Repeat Expansion Diseases

Dr. Wang described his laboratory's research program, encompassing proteomics, DNA damage and repair, and epigenetics and epitranscriptomics. He said the emphasis of his presentation would be on nucleoside repeat expansion in neurological diseases.

He noted that there are approximately one hundred CAG repeat expansion diseases, including Huntington's disease. A higher repeated length correlates with increased incidence and severity of disease. He listed proposed mechanisms of neurotoxicity arising from CAG repeat expansion.

Dr. Wang provided details about his group's work showing that:

- m^1A in CAG repeat expansion RNA binds to TDP-43 and induces neurodegeneration
- m^6A in CAG repeat expansion RNA modulates repeat-associated non-AUG (RAN) translation

His first hypothesis was that nucleosides in repeat expansion RNA may be modified, and the modification frequency may be influenced by repeat length. He provided data from several studies supporting the hypothesis. His second hypothesis was that modified nucleosides in repeat expansion RNAs may modulate their interactions with RNA-binding proteins. He noted that TDP proteinopathy is found in many neurological diseases, including Huntington's disease, amyotrophic lateral sclerosis, and frontotemporal lobar degeneration. His third hypothesis was that m^1A modification in CAG repeat expansion RNA may facilitate RNA-templated TDP-43 protein aggregation, thereby leading to TDP-43 proteinopathy.

Regarding m^6A, his hypothesis was that modified nucleosides, especially m^6A, in CAG repeat expansion RNA may promote RNA translation through a similar mechanism as cap-independent translation. He described dynamic modulation of m^6A by its writer and eraser proteins, along with other data on the role of METTL3. One study showed that

pharmacological inhibition of METTL3 led to reduced RAN translation from CAG repeat RNA.

In summary, Dr. Wang said that:

- RNA translation from CAG repeat RNA occurs through a similar mechanism as cap-independent translation, and is promoted by m^6A in CAG repeat RNA.
- It is important to examine whether RNA modifications also contribute to RAN translations from other repeat expansion RNA (e.g., G4C2 RNA).

Dr. Vasquez suggested that Dr. Wang may want to include DNA in a hairpin in his model as that is where the longer repeats start, so that it is known that those CAG repeats from hairpins and are processed aberrantly, leading to expansions and often deletions as well. She asked if methylation of adenine in the CAG repeats impacts expansion. She also asked Dr. Want to explain the repeat length requirement for protein interaction. Dr. Wang explained that the mechanism underlying the repeat expansion is actually highly associated with DNA repair.

Dr. Begley asked if Dr. Wang had any insight on when the methylation of RNA is occurring; whether it is during an R loop formation, and whether he had any insight on modification of the Cs in those repeats. Dr. Wang replied that they don't know where it happens as yet, but will be very interested in exploring.

VI. Oncogenic Rewiring of the Genome in Response to Environmental Cues

Dr. Fondufe-Mittendorf's research explores oncogenic rewiring of the genome in response to environmental cues, mainly through the model of environmental arsenic exposure, which is associated with cardiovascular disease, diabetes, and cancers such as bladder, prostate, colorectal, skin, and lung.

She stated that arsenic carcinogenesis is an epigenetic disease, in that inorganic arsenic (iAs) alters gene expression to promote cancer development, via iAs-mediated chromatin changes. She provided details about the cellular processes involved in iAs transformation, representing a model for how arsenic might directly or indirectly change the epigenome to drive cancer. For example, her group's studies have shown that inorganic arsenic inhibits the binding of CTCF to weak CTCF binding sites by targeting the 11^{th} C3H1 zinc finger. CTCF is important in the formation of the 3D chromatin structure. Differential expression of histone H2B variants also plays a role in altering chromatin structure. H2B variants are dysregulated in cancer. Canonical H2B and its variants exhibit unique mutational signatures.

These findings are part of an emerging new field of the oncohistone. Although they differ by just a few amino acids, they can drive specific cancers.

Circular RNAs are also important. Circularization occurs through backsplicing, an alternative splicing event. CircRNA expression is altered during iAs carcinogenesis. Data show that circSATB2 seems to be protecting the SATB2 transcript, and that SATB2 overexpression targets similar KRAS pathways as in iAs transformation. Dr. Fondufe -Mittendorf displayed a possible model for circSATB2 function, including iAs-mediated transformation.

Ultimately, an understanding of iAs-mediated changes in chromatin structure at the 1D, 3D, and nuclear integrity level is critical. Toxicology allowed the discovery of novel chromatin regulators and function.

VII. Single Cell and Spatial 'Omics to Understand Environmental Impacts on Breast Cancer Disparities

Dr. Justin Colacino from the University of Michigan School of Public Health described his work using single cell and spatial omics to understand environmental impacts on breast cancer disparities.

He said it is still early days in the use of single cell analyses in environmental health sciences, and single cell epigenomics is very much a developing field. He provided information about substantial disparities in breast cancer survival, and noted that attention has begun to coalesce upon the different subtypes of breast cancer, such as basal-like (also known as triple negative), which disproportionately strikes African-American women.

Breast cancer is a disease of dysregulated development, in that cancer cells use the same key regulatory pathways as embryonic development, but they are turned on at the wrong time. They exhibit similar behavior to stem cells during progression and metastasis. Aggressive cancers such as basal-like exhibit more stem like of cellular plasticity characteristics.

Dr. Colacino described the major cell types in the normal mammary gland, including breast stem cells. Analyzing those cells was one of the first single cell studies, and subsequent analyses showed that the different clusters revealed distinct expression signatures. Further experiments characterized basal/luminal hybrid cell populations which increase in abundance dramatically with age. Those cells have the highest correlation with basal-like breast cancer. It has been shown that aggressive breast cancers are characterized by cellular plasticity and dysregulated stemness. That understanding sets the stage for single cell analyses to seek to understand the biological factors at work.

He listed the investigated causes of breast cancer disparities, including genetics, obesity, racism and others. His lab has been investigating the role of environmental exposures, such as chemical exposures, which are not distributed equally. One study depicted the role of exposure disparities in non-Hispanic Black women.

Dr. Colacino showed examples of single cell and spatial tools available for EHS studies, which include well-based and droplet-based methods for single cell work, and morphomics, antibody-based, sequencing-based, and *in situ* hybridization-based methods for spatial analyses. He described challenges and concerns in single cell and spatial studies:

- Modest effect sizes of transcriptional changes
- Limited ability to detect lowly expressed genes
- Biological replicates are costly
- Sampling handling can be challenging
- Batch effects can compound data analysis
- Data analysis complex and rapidly evolving

He went into more detail about morphomics, or high-content imaging, as a high-throughput single cell analysis tool in EHS. It can provide very in-depth morphological profiles on many cells. It can look at cell structures, cell state markers, and it can provide epigenetic readouts. As an example, he showed the use of high-content imaging to quantify the luminal/basal state with toxicant exposures. He also described droplet-based methods, such as genetic multiplexing. By example, he talked about an experiment investigating the effects of bisphenols on normal mammary stem cells from diverse donors at the single cell level. Using single cell gene set enrichment analysis, it is possible to see that low dose BPS enriches for embryonic stem cell and basal breast cancer gene signatures.

One of the next steps will be the use of single cell multiomics, allowing multiple layers of omics from a single cell, such as simultaneous profiling of mRNA and chromatin from a single nucleus. This may illuminate several fundamental questions:

- What epigenetic program(s) drive these “hybrid” states?
- Which transcription factors are activated in cellular plasticity programs?
- Do environmentally induced hybrid/stemness mimic basal breast cancer epigenomes?
- Are the epigenomic programs activated in hybrid cells the same as those involved in epigenetic “aging”?
- How do signals from the microenvironment promote and stabilize these hybrid cells?

He described the sequencing-based approaches, which will have high applicability in EHS and toxicology. He explained the different methods and uses, such as SPARK for identification of spatial DEGs and CARD from spatial cell type deconvolution and gene expression imputation.

Dr. Colacino showed a graphic illustration of the field, from environmental exposures to the various types of data single cell and spatial analyses yield, allowing evaluation of environmental drivers of aggressive breast cancer programs like phenotypic plasticity.

VIII. Mechanisms of Transgenerational Inheritance of Obesity Epiphenotypes in Mice

Dr. Victor Corces from Emory University described his group's work investigating mechanisms of transgenerational inheritance of obesity epiphenotypes in mice.

He noted that inherited diseases may have a non-genetic origin caused by environmental effects resulting in germline epimutations. He said there are many examples of the phenomenon, and provided more detail about one in particular: autism. Only about 18-20% of cases have a mutation in the almost 1,000 genes that have been identified as being responsible for autism in humans. The other 80% are unexplained, and it is possible that epigenetics plays a role.

Dr. Corces discussed the transgenerational inheritance of epigenetic effects. In an experiment involving pregnant female mice who were exposed to BPA during germline reprogramming, the F1 generation was not obese, but the F2 and F3 generations were obese. This transgenerational epigenetic effect of an obese phenotype can be transmitted through both the male and female germlines.

He showed results depicting six instances of transgenerational inheritance of BPA-induced obesity. The effect was most pronounced in the F4 generation, but reverted to being similar to control mice in the F7 animals. F4 mice had a much higher food intake than controls, indicating that the BPA exposure affects something controlling appetite. He said that the most obvious explanation for the epigenetic memory of obesity among the different generations is DNA methylation. There is an interplay between DNA methylation and transcription factor binding.

He described the results of experiments looking at interactions at BPA-induced CTCF sites. There were 12 sites that were different in BPA and control. The CTCF site in the gene *Fto* was present in both sperm and oocytes, suggesting that this site is responsible for transgenerational inheritance of obesity. *Fto* is a gene associated with obesity in humans. *Fto* encodes an m6A RNA demethylase, and mice exposed to BPA have increased m6A methylation in an enhancer RNA that controls expression of *Fto*

and other genes. Mice in which the CTCF site in the *Fto* gene was deleted did not have increased appetite and did not become obese after exposure to BPA.

In conclusion, Dr. Corces mentioned that:

- Exposure of pregnant females to BPA results in changes in TF binding that are transmitted to subsequent generations in a manner that correlated with the transmission of obesity.
- BPA-induced binding sites may represent enhancers that are active in target tissues to alter gene expression and elicit novel phenotypes.
- *Fto* seems to be responsible for both the transmission and the adult phenotypes by acting early in development or in the adult target tissues.

IX. tRNA Modifications and Environmental Stress Response

Dr. Tom Begley from the RNA Institute at SUNY Albany discussed his lab's work on tRNA modifications and environmental stress response, stating that the "The Epitranscriptome is a Dynamic Regulator of Translation." They use computational, cell, and animal-based systems to build rules for gene regulation. The particular interest is how cells respond to reactive oxygen species, which can lead to lipid peroxidation, protein oxidation, enzyme degradation, and DNA damage.

He highlighted the central dogma of molecular biology, which is a blueprint of how genes are coded and turned into mRNA and protein. From an environmental exposure perspective, the interest is in when genes are turned on and how much of the gene is actually being made into a working protein. The epitranscriptome can control the "when" and "how much" of translation. He said he would focus on tRNA, the most heavily modified nucleic acid, each species of which has 8-12 different RNA modifications. Each organism has at least 50 distinct RNA modifications in their tRNA. "What we wanted to do was develop a technology that would allow us to look at RNA modifications and mass, and we want to do this in cells that were growing happily or cells that were actually stressed," he said. He described the process of quantitative tRNA modification analysis, and noted that stress promotes specific reprogramming of the tRNA epitranscriptome in the form of coordinated increases and decreases in specific modifications. Each toxicant producing stress has a specific modification profile of changes. Also, families of stress response genes possess unique codon biases. In response to stress, the tRNA epitranscriptome drives codon-biased translation.

Dr. Begley described the various technologies in use to analyze translational regulation by the tRNA-based epitranscriptome, such as mass spectrometry and sequencing techniques. Integrating the multiple systems leads to a systems-level mechanism. The codon-biased translational regulation was first established in budding yeast, but Dr.

Begley's group and many others have extended the translational regulation response to stress to other yeasts, infectious disease, parasites, cancer metastasis, and also human cells. He provided details about his group's work exposing mouse embryonic fibroblast cells to environmental tobacco smoke. That stress induces many RNA modification changes in the cells. He also presented data on several studies involving epitranscriptomic reprogramming required to prevent stress and damage from acetaminophen exposure. Acetaminophen exposure in liver cells induced dramatic changes in the tRNA epitranscriptome.

Dr. Begley depicted a method developed to help make sense of the data produced computational approaches that use gene-specific codon metrics. It produces codon-signature QR codes that lead to tRNA modification signature hypotheses.

Dr. Archer asked Dr. Begley if there is feedback in terms of regulation of the modification, citing the massive impact on translation in the Q example Dr. Begley had described. Dr. Begley replied that there is feedback, including transcriptional feedback.

X. RNA Substrate Recognition by Modification Enzymes

Biochemist and structural biologist Dr. Yunsun Nam from UT Southwestern discussed her group's work on mechanisms of tRNA methylation, focusing on RNA substrate recognition by modification enzymes. She noted that RNA is important in responding to the environment, and its function depends on many factors, such as RNA sequence, modification, folded structure, and localization/interactions, all of which lead to a biological outcome. She said her lab is interested in how RNAs and proteins interact with each other. RNA modification gives it a portion of its identity, which affects the biological outcome. Her presentation focused on how RNA sequence and structure affect the modification process.

The RNA-protein complex is dynamic and complex, and her lab focuses on specificity, modification efficiency, affinity, and regulation of the process. She discussed the METTL1-WDR4 complex's effect on tRNAs. The proteins combine to create m^7G modifications, leading to tRNA stabilization. Both proteins have been associated with human health. METTL1 amplification is seen in various cancers, and WDR4 mutations have been found in children with brain malformation disease. Both too much and too little methylation can cause disease.

Dr. Nam showed cryo-EM structures of the proteins, along with a view depicting rigid docking when they come together. She then presented several views showing various aspects of tRNA shape recognition and METTL1-WDR4. She explained that small change in the modification machinery can change the tRNA profile, and that can affect biology.

RNA recognition can depend on sequence or structure. The remainer of her talk focused on structure recognition. She discussed m^6A, the most abundant modification for mRNAs, which is known to affect RNA stability, translation, splicing, and perhaps chromatin. METTL14 is the major modification enzyme responsible for most of the m^6A modifications in mRNAs. The cancer mutation of METTL14, R298, increases cell migration and invasion and promotes tumorigenesis. She described how mutant METTL14 affects RNA sequence preference, changing intrinsic RNA specificity. She displayed a model for RNA substrate recognition by METLL3-METTL14. She also listed pathways affected by R298P, including canonical pathways and diseases/functions. Thus, METTL14 mutation changes RNA methylation sequence preference. This illustrates dynamic crosstalk between RNA and protein, showing that differential RNA modification correlates with diseases, and RNA modification can change dramatically with a single amino acid modification.

Dr. Begley commented that Dr. Nam's work highlights the complexity of the state of the field. She mentioned that it would be great if someday the rules for modification could be known.

Dr. Holian said that the structure/activity relationships Dr. Nam spoke about drive the interactions to regulate what is going on, but also goes to many other aspects of biology, whether it is particles interacting with membranes or others, that is what defines it. It is critical to know how it happens and the consequences. He asked Dr. Nam how this knowledge could be used to develop therapeutics. She replied that the mutant model she had shown can distinguish between small molecules, so her group has a small molecule screen to identify inhibitors of the enzyme. That is one type of strategy for developing therapeutics.

XI. Integration of Multi-omics Data

Dr. Ting Wang of Washington University in St. Louis briefed the Council on efforts to integrate multi-omics data. He went over the history of the Human Genome Project (HGP) and the timeline of developments in the field, including the reference human epigenome. He discussed the various omics technologies, and described the technologies used in the field, as well as the many analysis tools.

Dr. Wang presented as a case study the use of integrative multi-omics on the "dark matter" of the genome. One of the surprises of the HGP was the discovery that coding exons only made up about 1.5% of the genome, whereas close to 50% was derived from transposable elements, regions which are repetitive, have long been under-studied, and are often considered "junk" DNA. Later, it emerged that the transposable elements are important parts of gene regulation. He referred to the classic agouti mouse example, which showed that "you are what your mother eats." The causal element is a

transposable, epigenetic factor. “One can only imagine how many diseases would have very similar mechanisms,” Dr. Wang observed. He cited several of his lab’s studies involving multi-omics research involving oncogenes or proto-oncogenes, exploring the role of epigenetic insult or misregulation in tumorogenesis, and how common the epigenetic mechanism is. In one study integrating epigenomic data from two large projects (Cancer Genome Atlas and Roadmap), they found that at least 50% of the tumors had at least one event they called “oncoexaptation,” involving a transposable element providing promoters. He added details about the process, citing the example of one oncogene. Transposable elements function as alternative promoters and produce protein isoforms. They drive cancer evolution genetically and epigenetically.

Dr. Wang transitioned to discussing the phenomenon from the perspective of translational application. The oncoexaptation is a cancer-specific event; therefore it provides a unique opportunity to target for therapeutics, potentially through the use of splice-switching oligos. In a preclinical model, his group has shown that the modality works well, halting the growth of cancer cells. Also, transposable elements can be used to derive tumor-specific antigens (TE-TSA). In the multi-omics study Dr. Wang described, 99% of the tumors had at least one TE-TSA candidate. This suggests the possibility of developing an off-the-shelf cancer vaccine cocktail. Ultimately, epigenetics is reversible and the epigenome is targetable, presenting an opportunity to target transposable elements for cancer therapy.

Dr. Wang described his experiences with many of the genomics consortiums in the field, including TaRGET, the Human Pangenome Project, and IGVF. He mentioned a new project, Multi-omics for Health and Disease, a collaboration between NCI, NIHGRI, and NIEHS. The consortium aims to advance the application of multi-omics technology to study health and disease in ancestrally diverse populations. The initiative is expected to produce consensus approaches, best practices, and standards that can be generalized across different diseases and populations.

XII. Council Discussion

With the time remaining on the day’s agenda, Council members discussed a variety of topics related to the mini-symposium.

Regarding the multi-omics approach, Dr. Woychik asked Dr. Wang how concerned he was with the heterogeneity of datasets. Dr. Wang agreed that it is “absolutely a big problem,” but at the same time presents an opportunity. New technologies such as single cell will begin to offer solutions, he felt. Reference panels will also play a role, he said.

Dr. Vasquez said her group studies repetitive elements. Regarding cell types, she asked Dr. Wang whether looking at so many different examples may cause them to

average out, masking effects. Dr. Wang agreed that is an issue researchers have been struggling with for many years. He said that when he started learning about epigenetics, instructors said “your epigenetics is only as good as how pure your samples are.” He said that one of the goals of creating reference panels is the ability to purify specific cell types. Dr. Vasquez added that transposable elements can also regulate replication and recombination, and almost certainly can stimulate generic instability, largely in the form of double-strand breaks and deletions. That could also contribute to transcription, but she asked Dr. Wang if he was interested in more than just transcription and regulation, because cancer clearly also involves mutations and genetic instability. Dr. Wang said the questions are clearly systems-level biology, so it will be important to collaborate. The work he presented is somewhat reductionist, he added. His work is powered by thinking about how the epigenome evolved and how transposons evolved during the course of evolution. He added that the integration part is exciting, but the challenge is how to truly track every parameter.

Dr. Penning said that the mini-symposium was a tour de force, and quite remarkable. He noted that much had been said about methylation, all of which is dependent upon a methyl donor, which is SAM, which gets its methyl group from folic acid. He asked for opinions on the importance of studying folic acid, for the interplay between diet and downstream effects. Dr. Begley said that in his studies, dietary factors were proving to be immensely important, and folic acid will be a key player in the thinking of the modification world. Dr. Penning’s second point was about DNA, and how gene residue should not be overlooked. He said there is a DNA epigenetic code, with a combinatorial capacity that should be considered as well. Dr. Begley agreed, and said it should be part of students’ training.

Dr. Mutlu asked Dr. Begley about replacing the q-base in the diet of male patients, and whether it makes any difference. Dr. Begley replied that he was not aware of any studies looking at that, but that it is a great question to ask. He added that there are some Q salvage pathways that can be used to bring it back into play in the cell, but whenever there is an antibiotic in use, changing the gut microbiome, it could change not only the q-base but also other things that could influence the epitranscriptome. Dr. Mutlu asked Dr. Colacino about whether there are any efforts to standardize sample preparation in single cell RNA sequencing. Dr. Colacino agreed that it is a big challenge, because the choices made in dissociations have substantial results in data variability. He said there are ways to get around the issue, including new methods such as the flex method, where you fix and then dissociate.

Dr. Vasquez discussed the complexity of the situation, and said that nucleotide pools also need to be considered. She felt that looking at enzymes that modify DNA and RNA may be easier to study, given that the range of possible modifications is so

overwhelming. Dr. Yinsheng Wang noted that DNA repair may be an approachable subject to study modifications.

Dr. Archer invited Dr. Corces and Dr. Fondufe-Mittendorf to comment on contributions of protein components to the nucleus, either histones or architecture of breakage material. Dr. Fondufe-Mittendorf acknowledged that there are variants, but their modifications are unknown. It is still a brand new area, trying to understand how those modifications could contribute to changes in gene expression. Much remains to be determined, she added. Dr. Corces said that an important question is why we have such specific phenotypes. Is it because there are changes genome-wide in DNA methylation, histone modification, RNA modifications? Are there genome-wide changes, but we only see a few phenotypes, because the other ones are not as important? Or are the changes very specific, in specific genes? If there is a sequence specificity where some environmental effect is affecting only a few sites in the genome, it has to be through a mechanism that recognizes DNA sequence, and that is DNA binding proteins or transcription factors. He added that CTCF is always present at different sites in the genome, and it is exquisitely sensitive to DNA methylation.

Dr. Vasquez asked Dr. Fondufe-Mittendorf whether the histone variant that altered the size of the nucleosome also altered the size of the linker region, and if so, whether there are more double-strand breaks. Also, she asked whether she had done nuclear probing, and whether there is more hypersensitivity to reagents, to nucleases within those altered nucleosome regions. Dr. Fondufe-Mittendorf said they had not done that. She said what she had shown was mainly within *in vitro* system, with nothing *in vivo* yet. She said the question is how a single amino acid change on histone is having such a major impact in different cells.

Dr. Woychik asked about the whole concept of the exposome, which is exploding in interest currently. He said that a critical element of the exposome is characterizing biological responses to multiple environmental exposures. There has been much interest in incorporating epigenetics into exposomics research. He said it is clear that epitranscriptomics is playing an important role, so it is not just modification of DNA. He asked for the group's thoughts about capturing epitranscriptomics data into the exposome framework. Dr. Miller said that as we get the exposomic-level analysis of the complex exposures, there would be value in having a functional readout of the exposome, and it would seem that the epigenome sphere would be a good place to help prioritize the exposures that have the largest impact on the epigenome. Dr. Corces said the issue is what tissues should be looked at in a cell-type, specific manner. It becomes a daunting challenge. Dr. Miller added that some of the work of the TaRGET consortium might be a good starting point. Dr. Begley agreed that the question is a daunting data analytics challenge, but liked the idea of connecting the exposome with the epigenome and using that as a filter to get to the epitranscriptome. Dr. Nam also agreed that the

amount of data is daunting, and said that in trying to establish correlation, quantitation is very important. Dr. Corces said that when measuring the epigenetic outcome of the exposome, it should be done in a cell type that stays with us, because we do not really know what we have been exposed to. Chemicals that last a long time in us can be measured. He said that T cells are with us a long time and would be a great target tissue to look at the exposome.

Dr. Tyson thanked the mini-symposium speakers for their participation. Dr. Balshaw added his thanks as well.

CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the determination that it concerned matters exempt from mandatory disclosures under Sections 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. The closed session adjourned at 5:00 pm, February 12, 2024.

REVIEW OF APPLICATIONS

The session included a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions and recommendations. Members absented themselves from the meeting during the discussion of, and voting on, applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect. The Council considered and recommended 525 applications requesting $199,356,967 in total costs. For the record, it is noted that secondary applications were also considered en bloc.

OPEN SESSION

The meeting was open to the public from 9:02 am – 12:36 pm February 13, 2024.

XIII. Report of the NIEHS Director

Dr. Woychik briefed Council on Institute developments since the September 2023 Council meeting.

He began by addressing budgetary matters. Because of the spending caps set by the law that increased the federal debt limit, NIH's appropriations probably will be essentially flat in FY2024 compared to FY2023, with an allowable 1% increase in FY2025. The funding caps make it difficult for Congress to increase funding for NIH in FY2024 despite the Administration's request in the President's Budget for a higher NIH total budget. Additionally, several members of the House majority pushed for deeper

cuts in the Federal budget. As a result, the House Appropriations Subcommittee bill included a reduction of the NIH budget of more than $3.7 billion, focused on several specific NIH Institutes and Centers (IC) and research program but leaves most IC budget levels flat compared to FY2023. The Senate Appropriations Committee bill included a small increase of $265 million to the NIH total budget for initiatives in several ICs, but like the House bill, it left most IC budget levels flat compared to FY2023. Because these two bills keep appropriations for most NIH ICs at the same budget level as FY2023 and the possibility of additional reductions from that level, NIH is preparing for the likelihood of tight funding in FY2024.

The government is currently on its third Continuing Resolution (CR) for this fiscal year, a "laddered" CR, which takes funding through March 8. It is intended to give Congress time after reaching a deal on a top line number for FY2024 funding to finish completion of all 12 of the FY2024 bills. Dr. Woychik noted that "flat is good," but it is challenging.

He recognized the Senate confirmation on November 9, 2023 of Dr. Monica Bertagnolli to be the 17th Director of the NIH. She had previously served as Director of the National Cancer Institute. He provided more information about Dr. Bertagnolli, and thanked Dr. Tabak for his service as Acting Director. He described Dr. Bertagnolli's vision for NIH, with an emphasis on collaboration, excellence, harnessing technology, and promoting trust in science. Her vision includes a new format for IC Directors' meetings. The guiding principles articulated by Dr. Bertagnolli are:

- Our work is not finished when we deliver scientific discoveries, our work is finished when all people are living long and healthy lives.
- NIH research encompasses the laboratory, the clinic, and the community. Patients are partners in discovery.
    - To tackle the most persistent and complex problems, NIH aims to bring more members of the public into the research enterprise as our partners in discovery.
    - Income, age, race, ethnicity, geographic location, and disability status should not be barriers to participating in research or to benefiting from research advances.
- Progress is accelerated when advanced scientific methods, such as new data analytics, are applied to data that includes everyone, and when new discoveries are rapidly and equitably adopted in clinical care.
- NIH is committed to harnessing the power of AI/ML to advance research across diverse fields, diseases, and scientific communities.
    - Advanced scientific methods, new data analytics and technologies are unlocking possibilities to harness data in ways that achieve faster and more definitive results.

- NIH has launched and will continue to launch innovative and ambitious initiatives to propel fusion of biomedicine and AI/ML.

Dr. Woychik reported on the status of the FY25-29 Strategic Plan. It is currently in the Analysis and Draft Phase, which will continue through August 2024. The next steps will be:

- Circulate draft goals for NAEHS Council review and comment
- Post draft for public comment in 2024
- Collect and compile comments for NIEHS Senior Leadership review
- Revise draft plan and circulate to Council for review/approval in June 2024

He turned to the 6 NIEHS emerging scientific priority areas, starting with environmental justice and health disparities, an area in which NIEHS has been a leader. Dr. Archer has been providing leadership in an NIH-wide effort to develop plans concerning environmental justice (EJ). The HHS secretary asked NIH to develop three specific strategic and transformative EJ actions: a Centers of Excellence in Environmental Health Disparities program, an Environmental Justice Scholars program, and EJ Training initiatives.

An important part of the role of NIEHS in EJ has been to act as coordinator and convener, which was exemplified by the November 30, 2023 Environmental Justice Action Forum held in Mebane, North Carolina. The forum addressed the EJ situation related to the Western Electric Tarheel Army Missile Plant in Burlington, North Carolina, a sprawling, deteriorating industrial site that has been abandoned for decades. The event gathered a wide variety of community members and government officials to identify EJ issues, identify roles and responsibilities, and develop solutions in order to remediate the site. Since the forum was held, the U.S. Army has begun excavating up to 300 tons of contaminated soil at the site. The intention is for the site to be cleaned and up eventually redeveloped.

Dr. Woychik reported on a 2-day virtual workshop sponsored by the National Academies of Sciences, Engineering, and Medicine in November, 2023. The workshop involved NIEHS and several other ICs, along with CDC/ATSDR, and was held to establish public health research and surveillance priorities associated with the East Palestine, Ohio train derailment in February, 2023.

Turning to the exposome, Dr. Woychik described an important meeting held December 3-6, 2023 at the Banbury Center, *Integrating Exposomics into the Biomedical Enterprise*. The expert attendees drafted a consensus definition of the exposome, and a common and an operational definition of exposomics. It was a significant milestone in the development of the emerging field.

NIH is in the process of establishing a Center for Exposome Research Coordination, to be funded by NIEHS and several other ICs. The center award is expected in summer, 2024. Exposome research will also be advanced by major recent activities regarding exposomics taking place in the European Union, such as the International Human Exposome Network (IHEN).

Dr. Woychik addressed developments related to Precision Environmental Health (PEH). The All of Us Research Program is one of the major initiatives in the field. Its mission is to "accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care for all of us." NIEHS has been joining forces with the All of Us Research Program, working to integrate environmental exposures into the program's data collection efforts. The NIH 27 IC directors, including Dr. Woychik, published a commentary in *Nature Medicine* (February 19, 2024) lauding the All of Us Research Program. The program recently awarded $30 million to the University of Colorado to establish a Center for Linkage and Acquisition of Data (CLAD), which will collect clinical, geospatial, and environmental data to address the program's considerable data needs. Another contribution to environmental understanding related to PEH comes from Personalized Environmental and Genes Study (PEGS), which collected data from approximately 9,400 participants in three surveys from 2013-2020. Several NIEHS researchers are part of the PEGS Executive Leadership Committee.

Turning to climate change and health (CCH), Dr. Woychik is Chair of the Executive Committee of the NIH Climate Change and Health Initiative, which recently added several new IC director members, reflecting the intense interest in CCH across NIH. He mentioned the 1st Annual Café Climate Change and Health Conference, which was held February 5-7 and included more than 1300 registrants who participated in panels, training, roundtable discussions, and networking. The Executive Committee recently approved a third round of funding for the Intramural Targeted CCH Program (ITCCH), which funds intramural researchers in the CCH area from across NIH. Additionally, the physiological effects of climate change will be explored through basic/mechanistic research involving two sophisticated climate enclosures to be built in the animal facility at NIEHS. Also, DIR is establishing a new NIH-wide intramural center dedicated to investigating the health impacts of climate change. Recruitment of a director for the center is ongoing.

Dr. Woychik proceeded to the mechanistic and translational biology/toxicology priority area. The most important development in that area over the last several months is the announcement of funding for a new Common Fund project called Complement Animal Research in Experimentation (Complement-ARIE). The objective is to develop human-based new approach methodologies (NAMs) designed to transform basic, translational, and clinical sciences. The program will be funded at $35-40 million per year for 10 years.

In conclusion, Dr. Woychik noted the selection of Dr. Heather Patisaul as Director of the Division of Translational Toxicology. She will join NIEHS on March 24, 2024.

He also briefly described his trip to India during the first two weeks of January, where he attended a meeting on exposomics and PEH. He also delivered lectures and attended several other meetings.

Dr. Hood thanked Dr. Woychik for his involvement in supporting East Palestine. Dr. Woychik said he was pleased with the progress of the all-of-government approach to helping the victims of the man-made disaster.

Dr. Hood asked him about progress regarding data integration efforts in the exposome. Dr. Woychik replied that there has been much progress and much discussion around NIH. He said it is clear that there is increasing interest in the exposome beyond NIEHS. There is general recognition that managing data needs to be done differently, and integrating environmental and exposomics data needs to be approached thoughtfully. He felt that the Banbury conference was a step in the right direction. Dr. Miller added that the conference showed that the other ICs who are interested in exposomics are aware of the need for coordination.

Dr. Hornbuckle expressed support for many of the goals being discussed in the strategic plan, such as examination of the exposome, linking to community engagement, management of data, and remediation of route of exposure to toxic compounds as seen in the Superfund Research Program (SRP). She said she was concerned about the opportunities for continuing SRP funding. Dr. Woychik said that the House proposal was not necessarily the budget that will be passed, and we must wait to see what happens March 8. He said he was perplexed by the possibility of defunding the program. He pledged to continue to “pound the pavement” for support for the program.

Dr. Penning felt that one of the biggest roadblocks in the exposome area is the need to get exposure histories into electronic health records (EHRs), and potentially getting the data into the All of Us biobank. Dr. Woychik said that the issue is a personal passion of his. Dr. Balshaw referred to the CLAD initiative to build out a research infrastructure as one way to address the problem. He added that the conversation around epigenomics and epitranscriptomics also should give hope about being able to bridge exposures and biological sample measures. Dr. Miller noted that residential and occupational histories are relatively easy to collect and could be added to EHRs, but the challenge is that often physicians do not know what to do with that type of information. Also, retrospective environmental exposure analysis is possible to be able to spot trends. Dr. Penning noted that many health systems use the EPIC EHR, and he wondered if there might be a top-down approach to adding fields to incorporate exposure information. Dr. Woychik

agreed that it would be important to integrate that type of information into EPIC and other EHRs.

Dr. Greenamyre pointed out that clinic time is quite limited and clinical demands are prohibitive, presenting another roadblock to the type of exposures consideration being discussed. Dr. Mutlu agreed. Dr. Greenamyre also pointed out that EPIC is mainly oriented toward capturing billing efficiently. Dr. Cormier suggested that perhaps the residence and occupation information could be captured from accounting records. Dr. Hood said that integration of the data will be inevitable.

Dr. Cormier added that the exposome is a fantastic idea, but it is mainly oriented toward capturing urban populations, while the rural populations are most vulnerable to adverse exposures and EJ issues. Dr. Hood pointed out that Justice40 covers both rural and urban populations. Dr. Woychik agreed that it would be very important to capture information from rural populations, particularly with the exposures related to agriculture. Dr. Miller pointed out that location is irrelevant to analyzing past exposures via blood samples. Dr. Cormier noted that many rural areas lack hospitals and clinics for blood sample collection, contributing to disparities. Dr. Woychik agreed that the issue needs to be addressed.

XIV. Report of the DERT Director

DERT Director Dr. David Balshaw briefed Council on DERT activities and accomplishments since the September 2023 Council meeting.

He related DERT staff developments, including the departures of Melissa Smarr, Ph.D. and Michelle Victalino and retirement by Liz McNair. Michelle Campbell, Krisalaun Battle, Francoise Santos, Tierra Tucker, and Ashley Vargas, Ph.D., have joined DERT. Ashley Vargas, Ph.D. has been appointed as Deputy Director of the Division of Extramural Research and Training. Michelle Heacock, Ph.D., is now Chief of the Hazardous Substances Research Branch, and Srikanth Nadadur is now Chief of the Exposure, Response, and Technology Branch. Program Analysis Branch Chief Christie Drew, Ph.D., will serve a digital NIH detail from February through July 2024, developing an inventory of IT tools that support grant-related business processes.

Dr. Balshaw introduced the annual statutory requirement for the council to approve delegated authorities—actions delegated to DERT staff that require no follow-up action with Council. The current list is:

1. Change of institution
2. Change of PI
3. Continuation of Grant with Interim PI
4. Extension Without Funds

5. Extension With Funds

He went over the suggested updates to the council-delegated authorities, which were minor updates to language to be consistent with NIH policies and best practices.

Dr. Penning moved to approve the authorities; Dr. Holian seconded. Council voted approval.

Dr. Balshaw provided a wrap-up of the FY2023 DERT budget. The division reviewed 1,274 applications. Of the 243 competing awards, 134 were research project grants (RPGs), 47 were Other Research Projects, 22 were SBIR/STTR grants, 8 were for centers, and 32 were training grants. The average RPG cost was $535 thousand for competing awards and $512 thousand for non-competing. The payline was at 10% for R01, R03, and R21 grants. The NIEHS success rate for R01s was 13.7% and for RPGs was 15.14%. FY2023 extramural grants totaled $444.4 million, with 66.1% ($294 million) going to RPGs. Of that total, $227.5 million was devoted to R01s. Of the 134 competing awards, 15 were solicited ($10.5 million) and 119 were unsolicited ($61.3 million). There were 433 non-competing awards ($222 million), most of which were R01s ($177 million). The Superfund funding in FY2023 totaled $78.4 million, with $27.3 million devoted to the Worker Training Program and $51.1 million to the Superfund Research Program.

He presented data that he termed “a story of success” by improving the timing of DERT awards throughout the year. In 2023, more than 80% of the grant awards were completed by the end of July. This has resulted in the grants management staff no longer needing to work overtime to get awards out the door, and staff members were able to take family vacations in the summer for the first time.

Dr. Balshaw described DERT initiatives for FY2024, which total $65.55 million. They include programs such as ONES and the Centers for Oceans and Human Health. He discussed the NAEHS DEIA Working Group, which was convened in 2021 to be advisory to Council on matters related to racism, diversity equity, and inclusion, and was chaired by Dr. Vasquez. He listed the subcommittee’s accomplishments, including recommendations planned for 2024, with the assistance of a new DEIA contractor.

Dr. Balshaw concluded with a summary of DERT meetings since the last Council meetings and a list of upcoming DERT meetings.

Dr. Vasquez asked Dr. Balshaw to comment on the downturn in R01 applications this year. He said that there was a slight downturn in the total number of applications received across all mechanisms from 1,298 to 1.274 which is probably within normal variation, although it was somewhat surprising. He said it would be monitored going forward.

Dr. Penning asked about the increase in post-doctoral stipends, and what kind of planning is taking place to absorb that increase. Dr. Balshaw replied that it is a very active discussion across NIH, and it is anticipated that there will be guidance coming from NIH on how to proceed, with a number of strategies under consideration. Dr. Woychik mentioned that it is a subject of intense discussion and debate, as it has a huge budgetary impact. He assured that the IC directors and the new NIH director are on top of the situation.

Dr. Miller asked if there was any update on the ONES program. Dr. Balshaw confirmed that there is currently a pause on the program, while it is being evaluated and alternative strategies are being considered. NIEHS is taking stock of what strategies can be used to most effectively nurture all early stage investigators. Dr. Woychik added that ONES itself is not going away, but the implementation of ONES will be different, with more details coming in the near future.

XV. Update on Environmental Justice Activities at NIEHS

NIEHS Deputy Director Dr. Trevor Archer focused on the various EJ activities that NIEHS is undertaking and leading across NIH. He noted that NIEHS has an extensive history of supporting grant programs and research project to address EJ and health disparities. The institute established its EHD-EJ faculty as a cross-NIEHS interdisciplinary working group to increase understanding, build capacities, and promote environmental health equity. In recognition of NIEHS efforts in the area, NIEHS was tapped to lead a new cross-NIH EJ working group to coordinate and address EJ issues.

Many NIEHS extramural programs focus on EJ and EHDs. Intramurally, fundamental research addresses the issues, as well as community-engaged efforts of the Women's Health Awareness Community Resiliency, Environmental Action, and Collaborations for Health (REACH) program. Within the Office of the Director and Deputy Directors, there are efforts to coordinate and convene groups around timely and important topics.

Community engagement in EHS research has long been of critical importance to NIEHS. It is well known that it:

- Builds trust
- Inspires the next generation
- Raises environmental health literacy
- Builds capacity of ALL partners
- Advances environmental health research
- Informs health protective practices

However, it requires:

- Time
- Listening
- Respect of local knowledge, language, and culture
- Equity
- Humility
- Authenticity

Dr. Archer provided details about several of the programs NIEHS uses to address EHD and EJ priorities, such as the Research to Action Program, NIEHS-funded research centers, and Partnerships for Environmental Public Health (PEPH). Additionally, the Women's Health Awareness Community Engagement Program is an innovative environmental health research, public health practice and advocacy initiative within the NIEHS Division of Intramural Research. Its annual Women's Health Awareness event will be held April 13, 2024.

Dr. Archer described the Worker Training Program (WTP) within DERT, which trains workers, communities, scientists, and others to effectively respond to hazardous materials, waste and emergency response activities such as hurricanes and floods. Its component program, the Environmental Career Worker Training Program, focuses on recruiting un- and under-employed individuals from communities across the U.S. for a job training or pre-apprenticeship program. The WTP has had a tremendous economic impact, and is central to NIEHS's Justice40 efforts.

Dr. Archer described several of the NIEHS research initiatives to address EHDs and EJ, including studies involving uterine fibroids, social and environmental determinants of health, use of cord blood, and potential exposures near Superfund sites.

NIEHS sponsors community forums in cities across the nation designed to convene members of the public with NIEHS and other federal, state, and local government health officials, environmental health professionals, and disease and environmental advocacy groups. The recent Environmental Justice Action Forum regarding the Western Electric Tarheel Army Missile Plant, described earlier by Dr. Woychik, was a case study or model for an all-of-government approach to how a community action forum could be convened for other EJ communities. The forum included federal, state, and local government officials as well as a wide variety of community groups and members.

Dr. Archer provided more details about NIEHS EHD and EJ initiatives and programs, such as PEPH, Research to Action, and NIEHS-funded research centers.

The NIEHS EHD-EJ Faculty was established to advance NIEHS-wide focus priorities on environmental racism, EHD, and EJ. It works to:

- Foster integration of multiple disciplines to study environmental racism, EHDs, and EJ
- Understand the role of social determinants of health and how they relate to exposure and disease susceptibility
- Raise the profile of EHD and EJ research across NIEHS and NIH

Reflecting the deep well of commitment that NIEHS leadership and faculty have shown over the years in promoting EJ, Dr. Archer was chosen to lead the NIH Environmental Justice Working Group, which consists of 18 ICs and more than 70 participants. NIH was requested by HHS to develop three strategic and transformative EJ actions:

- Centers of Excellence in Environmental Health Disparities
- Environmental Justice Scholars Program
- Environmental Justice Training Program

Dr. Archer provided more details about the three proposed strategic actions.

Late in 2023, the NIH EJ Working Group issued an RFI seeking feedback on approaches that NIH ICs, Centers, and Offices could take to support research and capacity building efforts to advance EJ in the U.S. Some 41 responses were received, and the data is currently being analyzed.

In conclusion, Dr. Archer said that NIEHS is excited about bringing EHD and EJ into a trans-NIH framework, to expand capacity in the broader NIH context, in order to significantly lead and help lead colleagues as EJ continues to be a central feature in the work that NIEHS does.

Dr. Nez Henderson said she would be traveling to the Navajo nation to discuss for the first time in a public setting the forced relocation of thousands of Navajos from 1972 until recently. She said there was no research on the topic, and wondered if the NIEHS has done any type of work in the area. Dr. Archer said he was unaware of any research on the topic, but that the hope within the EHD-EJ program is to take from the affected communities identification of important areas that may not have been previously studied. He said he would be happy to take input about this specific subject. Dr. Nez Henderson spoke more about the spiritual and mental health impact of forced relocation. Dr. Archer said that studying those aspects would dovetail with greater appreciation of the importance of psychosocial stress and its impact on health. Liam O'Fallon thanked Dr. Nez Henderson for putting the subject forward, given the importance of indigenous knowledge. Sharon Beard mentioned that mental health and cultural competency issues are being looked at in the EJ training program. Dr. Ashley Vargas added that the nutritional sciences are now finally looking at the role of food in indigenous health, as well as its spiritual value.

Dr. Geller thanked Dr. Archer for his presentation, which described the full breadth of NIEHS activities in EJ and EHDs. He was particularly interested to have heard more about the program on women's health awareness. He said EPA would be interested in becoming involved in working on the issues. He directed participants to a link he had put in the chat box regarding an upcoming workshop on cumulative impacts. Dr. Archer thanked Dr. Geller for EPA having been a terrific partner for NIEHS, particularly in the Mebane community forum.

XVI. Update on the NIH-Wide Climate Change and Health Initiative

Dr. Vargas, who moderated this section of the day's proceedings, introduced Dr. Ashlinn Quinn from the Population Health Branch, who was recently added to NIEHS specifically to work on CCH.

Dr. Quinn provided background information and a general update on the NIH-Wide Initiative on Climate Change and Health, as mandated in 2021 by President Biden's Executive Order 14008. The initiative has included:

- Institute and Center Directors as NIH leaders
- Re-energized NIH Working Group of over 180 staff
- Coordination across NIH

In FY2023, NIEHS received a $40 million Congressional appropriation for CCH.

The NIH CCH Initiative (CCHI) Executive Committee is chaired by Dr. Woychik. It expanded from 7 to 11 NIH ICs in 2023. NIEHS is represented by Aubrey Miller (Steering Committee Co-chair), Gwen Collman (Strategic Advisor to the CCH Initiative), and Claudia Thompson and Ashlinn Quinn (NIEHS representatives to the Steering Committee). Dr. Quinn went over an extensive list of CCHI milestones in 2023.

She discussed the status of NIH extramural funding related to CCH from FY21-FY23, including both unsolicited and solicited grants. Unsolicited grant applications rose from 132 in FY21 to 276 in FY23. Awards grew from 27 ($11.5 million) in FY21 to 59 ($26.1 million) in FY23. Approximately 50% of the FY23 applications and awards are at NIEHS, with the other half spread among nine other institutes. Approximately 30% of the awards and 40% of the unsolicited applications were R01s. The solicited grants were devoted to:

- Alliance for Community Engagement – Climate and Health (4 awards)
- CCH Research Coordinating Center (1 award)
- P20 Exploratory Centers (5 awards)

Dr. Quinn described a new partnership program, a collaboration between NIH and the National Science Foundation (NSF). The program funds two centers at universities known for their disaster response expertise: University of Colorado Boulder, and the University of Washington. There are currently 12 NIH-funded CCH Research Centers.

Including CCH NOFOs in the FY21-FY23 grant analysis, including unsolicited applications, RCCs, and P20s, applications grew to 311 in FY23, with 65 awards.

Dr. Quinn went over NIEHS funding in CCH. She listed the main exposures of interest in CCH grants, FY21-FY23: air pollution, extreme weather and multi-agent/mixtures were the top three. She reviewed several examples that comprised multiple exposure categories. The main health outcomes of interest in the grants portfolio were (in order) morbidity/mortality, respiratory, birth outcomes, neurological, cardiovascular, reproductive, metabolic, and kidney. She described several examples of studies of CCH- related outcomes.

She provided details about other CCHI activities.

The NIH Intramural Research Program (IRP) in CCH employs a three-pronged approach. First, there is the NIH Intramural Targeted CCH (ITCCH) program, which to date has awarded seed funding to two cohorts of investigators across 8 NIH institutes. The IRP is also building infrastructure, including two climate enclosures to be housed at NIEHS. The IRP is establishing a new Intramural Center for CCH Research dedicated to investigating the health impacts of climate change.

Dr. Quinn described the NIH Climate and Health Scholars program. The inaugural class of 7 scholars for 2024 has been announced. She alluded to NIEHS-developed resources, including the CCH Literature Portal, the CCH Glossary, and the DR2 Portal. In March 2023, the NIH Climate and Health Outcomes Research Data System (CHORDS) started, with $4 million in funding from the HHS Patient Centered Outcome Research Trust Fund. The CHORDS goal is to empower health research through data resources linking climate, exposure, and health data.

Coming in 2024 will be:

- Relaunch of the NIH CCHI website (summer 2024)
- New round of awards for P20 Exploratory Center Development Grants
- More unsolicited applications under review
- Presence at meetings: European Commission CCH Conference (February, Brussels), ISEE (August, Santiago), etc.
- Working groups, interagency collaborations, and more

Dr. Penning mentioned that he is a member of the Intercenter working group made up of the P30 Environmental Health Core Centers on CCH, which meets monthly. He invited Dr. Quinn to present to the group. He noted that in her discussion of intramural CCH research, she had included references to use of electronic health records to get information on exposure data, biosensors, and biowearables, which he said could help facilitate association studies between people's exposures, emergency room visits, prescription data, and other information. Dr. Quinn said that across the initiative it is well-recognized that data integration is highly needed.

Dr. Hood said there are many areas of CCH research that need to be embellished and grown, such as implementation science, mitigation strategies, or what will move the needle with regard to policy change in local municipalities. As climate change comes to the forefront, EJ and vulnerable populations will be the most adversely impacted, aligning with the mission of the NIEHS, he said. Dr. Quinn agreed, and said that especially where climate change is concerned, the need to act is at the forefront of everyone's thoughts.

Dr. Vargas said that one of the things that makes NIEHS so special is community engagement. She wrapped up the session.

XIV. Adjournment

Dr. Balshaw thanked everyone who had been involved in the proceedings for a very productive Council meeting. He reminded Council members that the next meeting, June 4-5, 2024 would be in person. The September 11-12, 2024 and February 18-19, 2025 meetings will be virtual.

Dr. Balshaw adjourned the meeting at 12:36 pm, February 13, 2024.

CERTIFICATION:

Richard P. Woychik -S
Digitally signed by Richard P. Woychik -S
Date: 2024.05.13 10:08:44 -04'00'

Rick Woychik, PhD
Chairperson
National Advisory Environmental Health Sciences Council

David M. Balshaw -S
Digitally signed by David M. Balshaw -S
Date: 2024.04.18 15:18:21 -04'00'

David Balshaw, PhD
Executive Secretary
National Advisory Environmental Health Sciences Council

Attachment:

Council Roster